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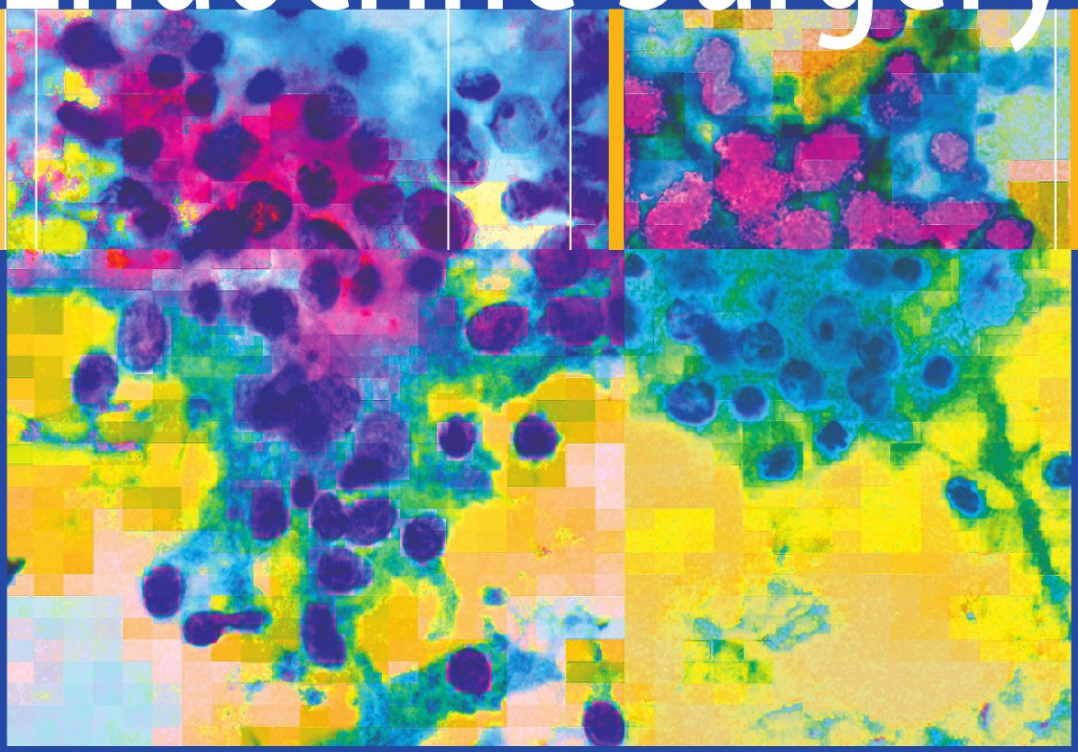
Endocrine Surgery



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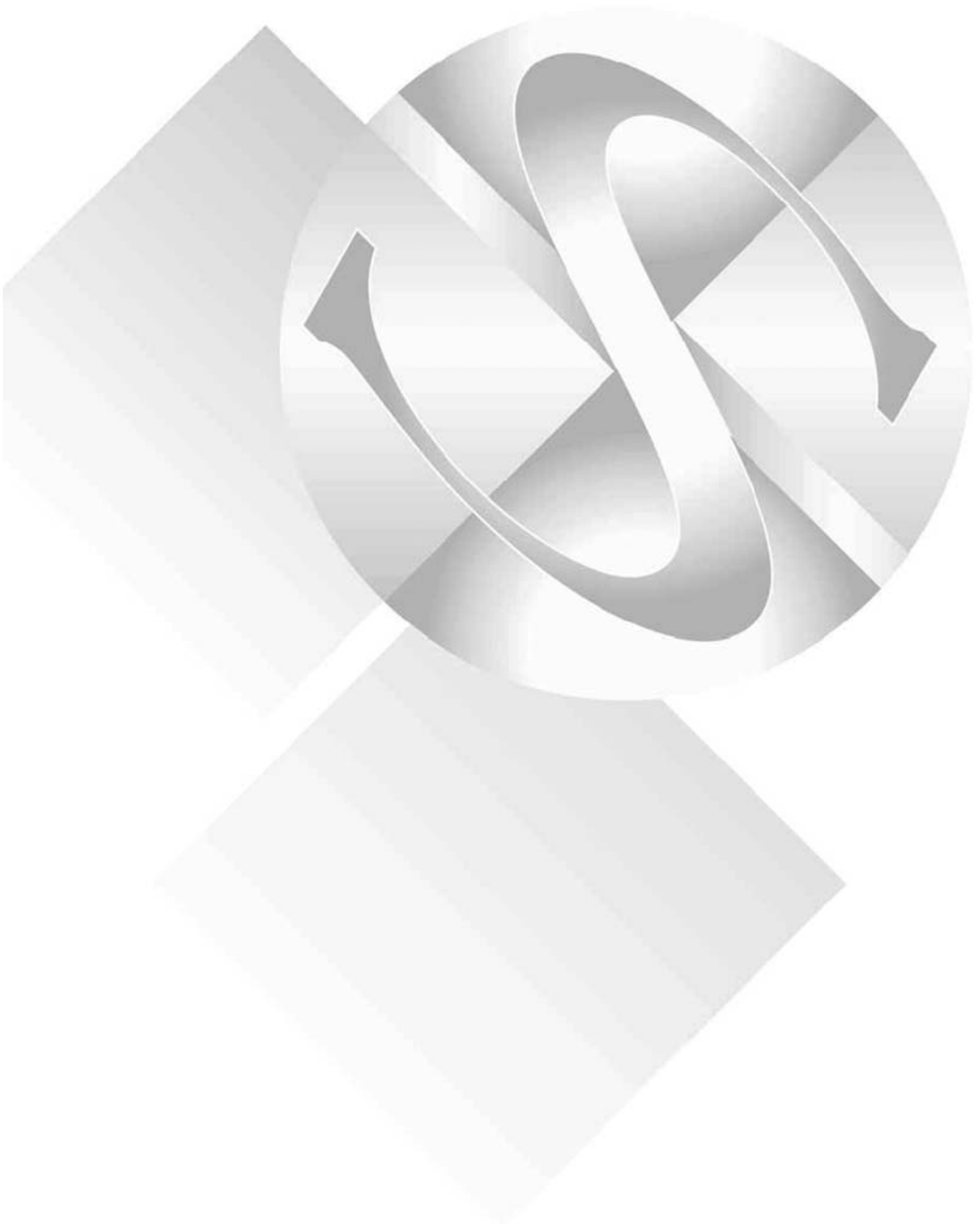

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Johnathan G.H. Hubbard, William B. Inabnet,
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Endocrine Surgery

Principles and Practice

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Foreword by: Jon van Heerden

Springer

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To my wife Kathleen, and children Frances and William, whose dedication and unconditional love keeps me motivated. And to my endocrine surgery patients, who allow me the opportunity to practice my profession with grace. WBI

To my late father, who inspired me to pursue a medical career, and to my wife, Sabrina, and my children, Bryan and Jenny, who have given me so much support. CYL

'For Chloe Margaux' JGHH

Foreword

This latest addition to the Endocrine Surgical library is a gem to be savored at leisure. It is a comprehensive review and is on the cutting edge of current knowledge regarding surgical endocrinology.

The fact that the three outstanding editors of Endocrine Surgery are from widely separated geographic continents (Europe, Asia and America) clearly establishes the flavor for this international contribution. The surgical arena and the endocrine surgical subspecialty, in particular, is truly international in scope, as it should be, and today represents a unique close knit family. This is a healthy phenomenon for it allows rapid and constant exchange of information and ideas by dedicated surgeons, endocrinologists, pathologists, radiologists, and researchers who personally know and respect each other, and who share a clear cut common goal – to simply do what is best for each and every patient afflicted with an endocrine disorder.

The astute reader of this encompassing collection of contributions will notice a "changing of the guard" phenomenon as well. Although there are well-known players in this endocrine surgical orchestra, there are, pleasingly, a number of less well-known (albeit for a short time only) contributors. This is very good indeed and is something that pleases me – a member of the old guard, immensely. The success of surgical education, and as a consequence, of patient care, is that each successive generation should be better and wiser than the preceding one. If this is not so, the previous generation has dismally failed. This compendium wonderfully demonstrates that the authors (the three all star editors in particular) have not failed in this mission and that the prior generation can be justifiably proud. The authors are the brightest intellects in endocrine surgery today. They are, one and all, better than their educators and mentors – they have raised the bar appropriately. This is good. It should please us all. Peruse this volume with pleasure and reflect on each of your obligations to the generations that shall follow you.

As a lifelong surgical educator, I am optimistic about the future of surgery. This optimism is, in part, based on the knowledge that our art is in the capable and trustworthy hands of Barry, Johnathan and Chung-Yau Lo.

Jon van Heerden

Preface

As we enter the twenty-first century, the field of endocrine surgery is poised for greatness. Although we must never forget that the fundamental principles of surgery were passed down to us from the pioneers of endocrine surgery, including such legends as Billroth, Halsted, Cushing, and the Mayo brothers, endocrine surgery is evolving continuously, in particular over the last several decades. In addition to technological advances, tremendous strides have been made in our understanding of the endocrine system, leading to improved diagnosis and treatment of various endocrine disorders. Genetic understanding of disease basis permits earlier diagnosis and curative treatment of hereditary thyroid cancer in infancy before clinical presentation. Localizing techniques such as radioisotope scanning and venous sampling allow accurate localization of endocrine tumors, while positron emission tomography and radioisotope scintigraphy provide a reliable method for diagnosis and surveillance as well as treatment of endocrine malignancy. Improved localization and intraoperative parathyroid hormone monitoring have led to an evolution in the treatment of hyperparathyroidism. In addition, the advent of laparoscopic surgery permits increased application of minimally invasive techniques in the field of endocrine surgery. Various intraoperative monitoring such as neuromonitoring potentially enhances the safety of endocrine surgical procedures.

In this setting, we present to you *Endocrine Surgery*, a book which encompasses these advances in endocrine surgery with incorporation of fundamental basic concepts and principles. The editors are active endocrine surgeons practicing in three different continents – Asia, North America, and Europe. The editors communicated by Skype conference calling and utilized Google documents so that the concept, design, and organization of the book occurred in real time. In a sign of the times, the quality of the book has been enhanced by an expert list of contributors to whom we are extremely grateful for their participation. We also believe that the collective worldwide experience from our international contributors should facilitate current understanding of the state-of-the-art practice of endocrine surgery in managing various endocrine surgical problems. We hope that you find this book informative and useful as we strive to perfect the care of our endocrine surgery patients throughout the world.

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Section 1
Thyroid

1

Thyroid Embryology, Anatomy, and Physiology: A Review for the Surgeon

Todd P.W. McMullen and Leigh W. Delbridge

The thyroid gland, an obligate structure in all vertebrates, is essential for normal development and metabolism. As a response to the varying maladies of the thyroid, surgeons have devised various techniques to extirpate part or all of the gland. Recent advances include new tools such as the ultrasonic dissector (Harmonic scalpel) and the electrothermal bipolar sealing system (LigaSure) as well as the application of minimally invasive and endoscopic techniques. As surgical approaches have evolved, so has our understanding of the genetics of thyroid morphogenesis and the biochemistry of thyroid function. This review integrates recent work on thyroid physiology with our present knowledge of thyroid development and anatomical variations.

Thyroid Organogenesis and Anatomy

Thyroid Embryogenesis

The thyroid gland is a composite of two different cell types, the follicular cells responsible for the production of thyroid hormones triiodiothyronine (T3) and thyroxine (T4), and the parafollicular C cells that produce calcitonin. Thyroid follicular cells (TFC) are recruited to the thyroid fate from the endodermal epithelium of the foregut. C-cell precursors migrate from the neural crest to the fourth pharyngeal pouch located symmetrically on both sides of the neck. Specification of these two cell types marks the beginning of the morphogenesis of the thyroid gland. The development of the thyroid, through anatomic studies in humans and genetic studies in mice, can be described generally in the following steps [1–6]. The first visible manifestation of the thyroid, the thyroid anlage, begins as a thickening of the endodermal epithelium in the midline of the primitive pharynx at embryonic day 20 (see Fig. 1.1). Cellular proliferation of the TFC results in a thyroid bud that begins to migrate caudally from the pharyngeal floor leaving a remnant of descent known as the thyroglossal duct. The developing thyroid will pass through, or adjacent to, the hyoid bone on its course to the trachea (day 30–40) and the migration process nears completion by day 45. Under normal circumstances the thyroglossal duct, which connects the thyroid to its pharyngeal origin (known as the foramen cecum), will disappear. Simultaneous to the thyroid migration process, the C cells within the fourth pharyngeal pouch have localized to a transient embryologic region called the ultimobranchial body (Fig. 1.1). From its lateral origin, the ultimobranchial bodies will migrate medially from either side of the neck. By day 70, the TFC and C cells that make up the mature and differentiated thyroid gland have now merged anterior to the cricoid cartilage on the trachea. The thyroid gland then begins

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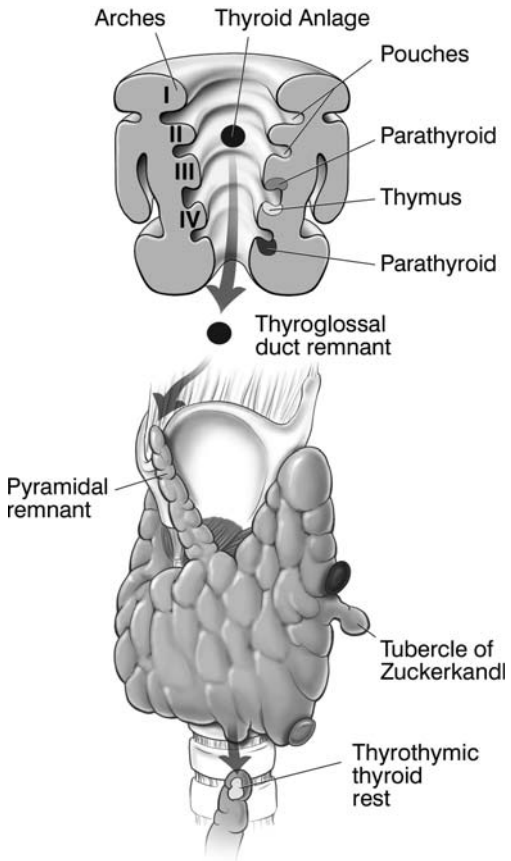

Fig. 1.1. Thyroid organogenesis. (*top*) A coronal section of the pharyngeal arch demonstrating the thyroid anlage and diverticulum forming. Laterally, the parathyroids and thymus derive from the third or fourth pharyngeal pouches. (*bottom*) As the thyroid diverticulum migrates caudally to its final resting position, the thyroglossal duct may persist and there may be an extensive pyramidal lobe along the line of descent. The parathyroids are localized generally as shown, with the superior glands migrating a shorter distance than the inferior glands. Thymic rests of thyroid tissue may also exist that may or may not be in continuity with the gland.

to expand and the TFC, which vastly outnumber the interspersed C cells, organize into follicles. The final dispersion of C cells within the thyroid is not uniform as they are concentrated within the middle and upper thirds of the lateral lobes of the gland [2, 7]. Functional differentiation of the TFC, and ultimately hormone production, is the final step in normal organogenesis. The proteins and pathways required for hormone synthesis are expressed once the thyroid reaches its final location on the trachea. Mice models demonstrate that T4 is present shortly after folliculogenesis begins and human fetal serum contains both thyroid-stimulating hormone (TSH) and T4 after 12 weeks.

Much of what drives thyroid morphogenesis, as described above, has been determined from a combination of studies on inherited disorders of the thyroid and mice models which are considered an excellent homolog for human thyroid development [1]. Summarized in Table 1.1 are the functional changes undergone by TFC, and the relevant controller genes, at the various stages of morphological development. The genes central to the morphogenesis of the thyroid gland and the functional differentiation of TFC are Titf1/Nkx2-1, Foxe1, Pax8, and Hhex [1, 8–12]. The simultaneous presence of these four genes is the hallmark of a differentiated thyroid cell. At the earliest stage of development, all four genes are required for the recruitment of TFC and organization of the thyroid bud. These genes will continue to drive thyroid development until the gland has completed migration and begins to enlarge. At this stage other genes are activated and pathways for hormone synthesis begin to develop (see Table 1.1). In the 10th and 11th week it is the serial expression of genes such as Fgfr2 and Tshr that prompts the production of thyroglobulin (Tg), thyroid peroxidase (TPO), and the TSH

Table 1.1. Thyroid Embryogenesis

	Functional differentiation			Controller genes			
Morphology	Tg, TPO, Tshr	NIS	Thyroid hormones	Titf1, Foxe1, Pax8, Hhex	Fgfr2	Tshr	NIS
Thyroid anlage	–	–	–	+	–	–	–
Thyroid bud	–	–	–	+	–	–	–
Expansion	–	–	–	+	+	–	–
Folliculogenesis	+	–	–	+	+	+	–
Hormone synthesis	+	+	+	+	+	+	+

Source: Data from De felice M, di Lauro R. Thyroid development and its disorders: genetics and molecular mechanisms. Endocrine Rev 2004;25:722.

receptor (Tshr) [1, 13]. By the 12th week the sodium-iodide symporter (NIS) gene is activated and soon after the NIS is found in thyroid cell membranes. This heralds the final step in cellular differentiation as thyroid hormone is detected in fetal circulation shortly after NIS expression (week 12).

Developmental Abnormalities of the Thyroid

Abnormalities in thyroid organogenesis, collectively termed thyroid dysgenesis (TD), may result in thyroid ectopy, hypoplasia, hemiagenesis, or athyreosis [14–16]. In certain cases of ectopy and hypoplasia, and in all cases of athyreosis (complete developmental failure), the production of thyroid hormone is impaired, resulting in congenital hypothyroidism (CH). Clinically, CH is manifest as impaired cognitive development and physical growth, and its phenotype is directly proportional to the duration and severity of the hypothyroidism [16–18]. CH is the most common endocrine disorder in newborns with an incidence of 1 in 3500 births in iodine-sufficient regions. Ninety percent of CH cases are due to some form of TD, while the remaining 10% are secondary to isolated defects in thyroid hormone synthesis [15, 16]. In cases of hypoplastic or ectopic thyroid glands, the function of the glands may or may not be disrupted significantly, depending on the overall cell mass. In many cases both hypoplastic and ectopic glands will demonstrate normal or near-normal levels of TSH and thyroid hormone with no clinical sign of impaired development [1]. Due to the complex relationship between thyroid function and morphology, studies of the prevalence of the varying types of TD in CH have documented discrepant results [1, 19, 20]. A recent review of studies using ^{99}Tc scintigraphy or ultrasound indicates that athyreosis and ectopy represent the vast majority of malformed thyroid glands [1]. Most cases of TD, regardless of phenotype, stem from isolated sporadic mutations but there is an inheritable component as relatives of patients with TD are 15 times more likely to exhibit a thyroid anomaly [1, 21, 22]. Interestingly, the type of thyroid anomaly will also vary in many types of related mutations. This suggests that mutations in a single gene such as Foxe1 (see Table 1.1) may account for multiple different phenotypic abnormalities including ectopy and athyreosis. There is also evidence for postzygotic events influencing pathogenesis as monozygotic twins do not demonstrate the same rates or types of TD [21]. Thus a single genotype may disrupt thyroid development at different stages of development causing varying phenotypes and clinical sequelae. The genetic mechanisms underpinning the major classes of thyroid developmental abnormalities are outlined below.

Athyreosis

Complete absence of TFC may stem from an early error in the formation of the thyroid bud or from a defect in the survival pathway of thyroid cells. Patients lacking a developed and functional thyroid gland may demonstrate only cystic remnants of the thyroglossal duct without any thyroid tissue [1, 16, 17]. However, other patients may exhibit thyroid tissue by ultrasound. A mutation early in proliferation can prevent the cells from completing differentiation to the mature thyroid cell capable of producing thyroid hormone. Gene knockout studies in mice have shown definitively that mutations to any one of the four key genes shown in Table 1.1 will result in athyreosis. When examining for the genetic mutations in humans responsible for these abnormalities, mutations to the *Foxe1* and *Pax8* genes were found in patients lacking a thyroid gland and Foxe1 has Mendelian inheritance (Bamfort–Lazarus syndrome) [1].

Hypoplasia

A hypoplastic but orthotopic thyroid gland is relatively uncommon. As in athyreosis, the hypoplastic phenotype may stem from a significant reduction in cell mass or there may be a metabolic defect in hormone synthesis limiting hormone production within the cells. A broad range of mutated genes including *Titf1/Nkx2-1*, *Pax8*, *Tshr*, *Hoxa-3*, *ET-1*, *Pax-3* are postulated to attribute to hypoplastic phenotypes [1, 15]. The *Tshr* gene is considered a consistent cause for the disrupting glandular growth in humans and over 20 different mutations have been found in familial cases of hypoplasia [1]. In certain mutations of the *Tshr* gene, the cells

fail to respond to the TSH-mediated signal for proliferation and gland expansion. Other mutations will disrupt TSH-mediated signals in thyroid hormone synthesis. Thus different mutations in the *Tshr* gene may demonstrate subclinical, mild, or severe degrees of hypoplasia with a broad spectrum of variation of TSH and T4 levels in affected individuals.

Hemiagenesis

In a unique subset of patients with reduced thyroid mass, it is the left lobe that fails to develop. Known as hemiagenesis, these patients are uniquely different from those with hypoplasia because the function of the gland is not significantly disturbed with both TSH and thyroid hormone levels remaining in the normal range [1, 23]. In studies using ultrasound, hemiagenesis may occur in 0.05–0.2% of the population [23]. It is unclear in humans which genes may be responsible, but in mouse models heterozygous for both *Titf1*$^{+/-}$ and *Pax 8*$^{+/-}$ genes, hemiagenesis of the thyroid has been documented [1].

Ectopic Thyroid

Ectopic thyroid glands represent the largest single group of TD and perhaps are the most heterogenous in terms of morphology [1, 24–27]. Thyroid ectopia is subject to all pathology of a normal gland and should be considered in surgical approaches to thyroid disease. Ectopic thyroid may rest anywhere between the foramen cecum superiorly and the mediastinum inferiorly. In most cases, the ectopic tissue is a midline position above the hyoid bone. Known as the lingual thyroid, the gland usually functions normally. Less frequently, the gland may descend and come to rest above or below the hyoid bone and may even be present within the trachea. Moreover, isolated rests of thyroid or prolonged extensions of the thyroid lobe may also be found in the thyrothymic tract. These thyrothymic rests were identified in more than half of the surgical specimens analyzed by Sackett et al. [28]. Lateral ectopic thyroid tissue, for example, in the submandibular region, has also been documented [1, 26]. This was postulated to be a consequence of defective migration of a lateral thyroid component from the ultimobranchial body [2, 26]. However, there is little evidence supporting follicular cell derivation in the ultimobranchial body [1]. It is more likely that the lateral derivation of thyroid does not exist and the observed "lateral" ectopic tissue is actually a disordered remnant of the median thyroid anlage [1]. Not limited to the neck or mediastinum, ectopic thyroid tissue has been reported in locations including the heart, duodenum, and ovaries [27, 29–31]. Outside the neck and mediastinum, it is unlikely for abnormal migration to account for thyroid ectopia. Thyroid tissue in the abdomen and other compartments is likely resulted from aberrant differentiation of uncommitted cells [1]. The genetic mechanisms behind ectopic tissue are unclear, and in humans no single gene has been characterized as a causative factor. In mouse models, selective disruption of the *Foxe-1* gene leads to abnormal migration and subsequent ectopic thyroid [1].

Abnormalities of Thyroid Migration

Normally, after migration of the thyroid to the cricothyroid, the thyroglossal tract obliterates by day 30–40 of gestation. However, in a significant proportion of the population, the thyroglossal duct persists [1, 32, 33]. Due to varying degrees of incomplete ablation, the midline thyroglossal duct remnant will vary in size and location from the foramen cecum to hyoid bone. In the largest reported series of patients, 60% of thyroglossal duct cysts were located adjacent to the hyoid bone, 24% between the hyoid bone and base of the tongue, 13% distal to the hyoid bone, and the remaining 3% intralingual [32]. The pyramidal lobe is another anomaly of thyroid descent with TFC extending up to, and sometimes beyond, the hyoid bone. This midline remnant may represent a small outcropping of tissue barely distinguishable from the gland, or it may extend up along the laryngeal cartilage and represent a significant fraction of the overall mass of the thyroid.

Anatomy of the Thyroid Gland and Related Structures

Driven by the perceived benefits of smaller incisions and less tissue trauma, significant effort has been applied to developing minimally invasive approaches to thyroid and parathyroid surgery. Reduced exposure requires a thorough understanding of the anatomical relationships of the thyroid gland to the structures at risk

during surgery, namely, the recurrent laryngeal nerve (RLN), the external branch of the superior laryngeal nerve (EBSLN) and the parathyroid glands. This review emphasizes recent studies on anatomical variations of these structures and their relationship to the thyroid gland [34–48].

Thyroid Gland

Under normal circumstances the thyroid gland rests on the anterolateral aspect of the cricothyroid and trachea. The boundaries of the thyroid gland are typically demarked posteriomedially by the trachea and esophagus, laterally by the carotid sheath, and anterolaterally by the overlying strap and sternocleidomastoid muscles. The gland itself has a bilobed shape and typically weighs 15–25 g, depending on sex and age. It also has an intervening bridge of tissue of varying sizes, the isthmus, connecting each lobe. The typical bilobed shape is preserved in most people but the size and symmetry of the thyroid can vary significantly and other anomalies can exist as follows. Superiorly, a pyramidal extension of the gland may be found on the anterior aspect of the cricothyroid. Laterally, the tubercles of Zuckerkandl, a consequence of median anlage and ultimobranchial body fusion, may form significant protrusions of thyroid tissue in the tracheoesophageal (TE) groove. The tubercle, which ranges from inconsequential to as large as 3 cm, can be identified in two thirds of patients undergoing thyroidectomy. Inferiorly, thyrothymic thyroid rests may be found in over 50% of patients [28]. These are classified by the nature of their connection to the main body of the thyroid and may be connected to, or completely distinct from, the gland. In pathological situation, the thyroid can enlarge and, in some circumstances, reach 100× its normal size. Enlarging glands may expand inferiorly into the thorax to become retrosternal and reach as caudad as the pericardium.

In terms of attachments and supporting structures, the gland itself has a capsule that is the extension of the pretracheal fascia. This capsule has extensions within the gland that form macroscopic lobules. The visceral fascia of the thyroid gland is attached anteriorly to the cricothyroid and thyroid cartilage. The Ligament of Berry affixes the posteromedial aspect of the gland to the underlying cricoids and tracheal rings. The thyroid is a highly vascular gland that has a redundant arterial supply from the superior thyroid artery (a branch of the external carotid artery) and the inferior thyroid artery (ITA) (a branch of the thyrocervial trunk) with abundant collaterals [38–41]. The arteria thyroidea ima is a relatively uncommon third arterial feed to the gland. Venous drainage is via three paired vessels, the superior, middle, and inferior thyroid veins that form a network of collaterals that can be quite impressive in pathology such as Grave's disease. Lymphatic drainage of the gland may extend superiorly to the delphian node or laryngeal nodes, inferiorly to the pretracheal nodes or laterally to the paratracheal nodes and cervical chain. Patterns of drainage based on sentinel lymph node studies indicate that the first regional draining bed is typically the central compartment followed by the lateral neck compartments [49]. Lastly, the gland is innervated with fibers from sympathetic and parasympathetic autonomic nerves that may alter aspects of thyroid function through changes in vascular supply.

Recurrent Laryngeal and Superior Laryngeal Innervation of the Cricothyroid

The RLN supplies the motor component to the intrinsic muscles of the larynx as well as the sensory innervation to the glottic larynx [38, 42–47]. Damage to this nerve can alter phonation and reduce volume as well as cause varying degrees of dysphagia. Knowledge of the path of the RLN in the neck is crucial to safe thyroid and parathyroid surgery. Originating from the vagus, the left RLN arises at the level of the aortic arch and courses through the TE groove to the insertion point in the cricothyroid joint. The right RLN follows the same description, but arises at the level of the subclavian artery. Both the right and the left RLN may run laterally or anterior to the TE groove, and the angle of the nerve relative to the trachea is usually more oblique on the right side. The right RLN may have a nonrecurring course (0.3%) and derive directly from the vagus approaching the cricothyroid directly without traveling in the TE groove. This is a consequence of a displaced

right subclavian arterial takeoff from the distal aortic arch. As such, a nonrecurrent nerve is not seen on the left except in cases of situs inversus. It is also important to note that communicating branches between the cervical sympathetic chain and the RLN are common (sympathetic inferior laryngeal nerve anastomotic branch or SILAB). They may be mistaken at surgery for a nonrecurrent RLN. Both left and right RLN may give multiple smaller branches to the trachea and esophagus as well as bifurcate or trifurcate prior to its entry at the cricothyroid joint. As the RLN ascends the TE groove, it crosses the ITA. In both surgical and cadaveric dissections the relations of the nerve and artery are complex and variable [43–47]. The RLN may run posterior, anterior, or between the branches of the ITA as illustrated in Fig. 1.2. Cadaveric dissections demonstrated 20 different configurations, but the results of these studies did not agree on the most common arrangement and there does not appear to be a propensity for a single configuration. The studies did agree that the arrangements were not necessarily symmetrical for the left and right sides in a given patient [42, 47]. Surgical series also demonstrated that variations in RLN and ITA anatomy should be considered normative with multiple branches of each structure compounding the complexity of this region [44–46, 50]. In devising methods to complete a safe dissection of the RLN, the tubercle of Zuckerkandl has been documented as an important landmark useful in its identification and preservation (see Fig. 1.2). The tubercle is situated on the posterolateral aspect of the gland in the TE groove in proximity to the cricothyroid membrane and thus is a relatively consistent landmark for the location of the RLN [48, 50, 51].

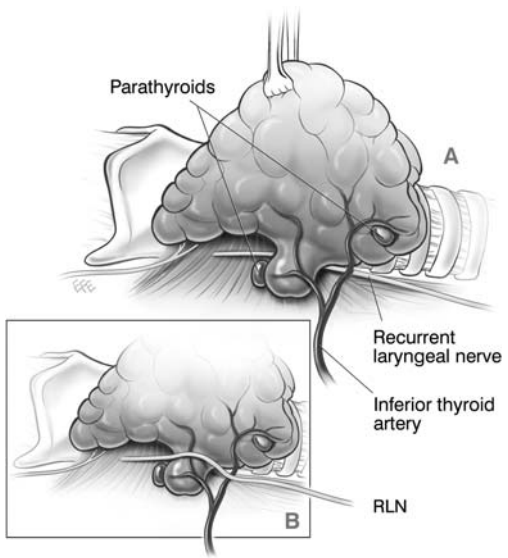

Fig. 1.2. (with kind permission of Dr Levent Efe, CMI) The path of the recurrent laryngeal nerve relative to the tubercle of Zuckerkandl and inferior thyroid artery is complex and may be completely posterior (**A**) or anterior (**B**) to these structures. There are multiple variations to these two extremes depending on the size of the tubercle and the branches of the nerve and artery. Note that symmetry is not necessarily maintained for right and left in a given patient.

The EBSLN serves as the primary innervation to the cricothyroid muscle, and it is essential in the production of high tones and modulating voice frequency. This nerve arises as a branch of the inferior vagal ganglion and descends along the pharynx travelling medially to the carotid then piercing the inferior constrictor muscle before running with the superior thyroid artery to innervate the cricothyroid muscle [52–58]. In virtually all patients there are also communicating branches between the EBSLN and the dorsal branch of the RLN (Galen's anastomosis). The significance of these are unclear and may represent sympathetic innervation although there is evidence of motor function. The proximity of the EBSLN to the thyroid gland has forced surgeons to devise techniques to minimize damage to this structure while ligating the superior pole vessels. Cernea and coworkers have completed anatomical studies to classify the major configurations of the nerve relative to the superior pole vessels [53–55]. Type 1 EBSLN are located more that 1 cm from the upper pole vessels and thus are not significantly at risk. However, Type 2a and 2b (see Fig. 1.3), comprising >1/3 of the configurations found anatomically, are within the range of dissection and may be disrupted with ligation of the superior pole vessels. As shown in Fig. 1.3b, Type 2b nerves are at considerable risk in that these nerves cross the vessels along the thyroid parenchyma. It is now understood that dissection utilizing the avascular space between the cricothyroid and the upper pole can reveal the EBSLN safely in >90% of cases and thus preserve its function [44, 50].

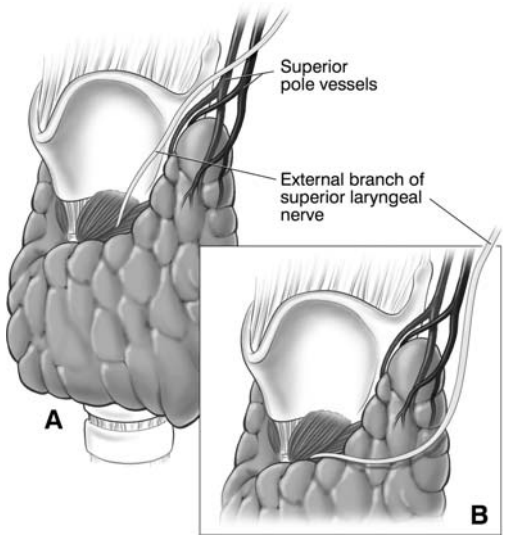

Fig. 1.3. The external branch of the superior laryngeal nerve as outlined by the Cernea et al. [53] For the Cernea classification 2a (**A**), the nerve is within the proximity of the superior pole vessels as it travels superiorly. In configuration 2b (**B**) the nerve is at significant risk during ligation of the superior pole vessels due to its anterior tract over the thyroid gland. Type 1 nerves are more than 1 cm above the superior pole and at decreased risk of injury (not shown).

Parathyroid Glands

The paired inferior and superior parathyroid glands are derived from the third and fourth pharyngeal pouches, respectively (see Fig. 1.1). It is this embryologic derivation and the subsequent migration of these pouches that accounts for the final location of these glands. These glands have been studied extensively in cadaveric dissections as well as surgical case series [59–62]. Approximately 85% of the population has four glands, with the remaining 13% having $\geq$5 glands and a small fraction having $\leq$3 glands. The paired superior glands, migrating a relatively short distance with the branchial bodies, are typically found on the posterior aspect of the middle third of each thyroid lobe, or in a juxtacricothyroidal position. A broader definition is that in 90% of people, the glands are located within 1 cm of the intersection of the ITA and the RLN [59]. The arrangement is typically symmetrical. The inferior parathyroid glands and the thymus migrate together and travel a longer path to their final position (see Fig. 1.1). The majority of inferior parathyroid glands may be found on the anterior or posterolateral aspect of the inferior thyroid lobe or within the thyrothymic ligament. In a fraction of cases the inferior glands may be in proximity to the superior parathyroids or as deep as the mediastinum. A recent surgical series of over 200 patients revealed that 16% had ectopic glands overall, with inferior glands comprising >60% of these cases [59]. Ectopic superior glands were most commonly retroesophageal or in the TE groove. Ectopic inferior glands were found primarily within the thymus, mediastinum, or intrathyroidal. The common origin of the parathyroids and thymus with migration toward the mediastinum is the cause for the more varied distribution of inferior parathyroid glands.

Thyroid Physiology

The hormone products of the thyroid gland comprise two different endocrine systems. Produced by the TFC, the thyroid hormones T3 and T4 are essential for fetal development as well as growth and metabolic regulation. Para-follicular C cells are responsible for the production of calcitonin which acts in concert with parathyroid hormone (PTH) and vitamin D to regulate serum calcium levels. The histologic organization of the gland is dominated by the TFC which organize into follicles with a central space full of colloid for storage of thyroid hormone.

Iodide Metabolism

One of the unique features of thyroid physiology is its requirement for iodine in the production of thyroid hormones. The importance of iodide metabolism is perhaps best illustrated by the work of Dobson [63], who postulated that incremental improvements in iodine trapping, leading to more effective thyroid hormone production, was an important evolutionary development in Homo sapiens. Clinically, an important relationship between iodine intake and thyroid disease has been understood for 150 years [64–68]. Iodine is an essential dietary requirement and deficient intake can lead to hypothyroidism, goiter, cretinism and malignancy. Equally detrimental is iodine excess which is associated with autoimmune thyroid

disease and papillary thyroid carcinoma. Iodine is efficiently absorbed within the gastrointestinal tract and concentrated within the thyroid gland for T3 and T4 synthesis [69]. The sodium–iodide symporter (NIS) is the intrinsic plasma membrane protein that couples movement of sodium and iodide into thyroid cells [70–72]. This energy dependent process, utilizing the gradient created by the sodium-potassium-ATPase within the basolateral membrane, is the key first step in thyroid hormone synthesis (Fig. 1.4). The structure of the NIS has been elucidated and much effort has been expended at understanding the mechanisms that regulate its activity. The primary regulation of this symporter is via TSH stimulation and serum iodine levels [73, 74]. The action of TSH on follicular cells, through multiple pathways, results in increased biosynthesis of the NIS as well as increased localization of the protein in the follicular plasma membrane. Increasing iodine levels will also stimulate uptake through the symporter. Wolff and Chaikoff demonstrated that progressively increasing levels of plasma iodine can reach a threshold that effectively stops organic binding of iodine and shuts down production [75]. After a period of adaptation the normal hormone synthesis resumes. The Wolf-Chaikoff effect appears to be a regulatory mechanism to protect from iodide overload and the process is mediated by the regulation of NIS activity. The NIS allows the concentration of iodide within a TFC to be 20–40 fold greater than that of the serum and thus >90% of the total body iodide is contained within the thyroid. The function of the transporter is important not only in the normal gland but in thyrotoxicosis and thyroid cancer. NIS mediated uptake of radioactive iodine is a key feature in ablation of the gland and disruptions to the function of this symporter, through mutations or metabolism, limit uptake of iodide and can impair I^{131}-mediated ablation.

Once the iodine is transported into the follicular cell it is rapidly oxidized and moved to the apical surface of the cell and incorporated into vesicles by the membrane protein pendrin (Fig. 1.4). Pendrin is found mostly within the thyroid and is the only membrane channel known in apical iodide transport [74]. The process and control mechanisms for pendrin are less well known but TSH is again considered the key regulatory molecule. Thyroid hormone synthesis continues on the apical surface of the cell.

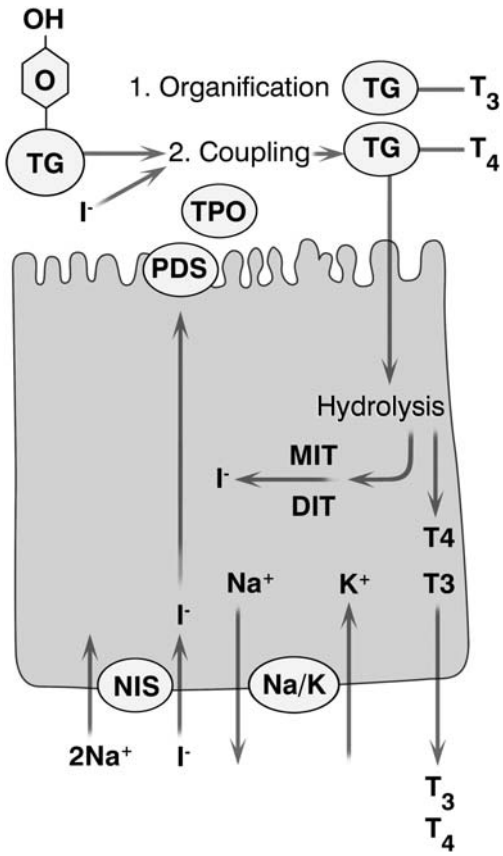

Fig. 1.4. Schematic diagram of the process of thyroid hormone synthesis beginning with the transport of iodine into the cell via the sodium-iodide symporter (NIS). The symporter utilizes the Na^+ gradient created by the Na^+/K^+ ATPase active transporter. Movement of iodine to the apical membrane and then incorporation into vesicles by pendrin (PDS) allows for coupling of iodine to the tyrosyl residues of the thyroglobin protein also at the apical surface. This reaction, termed organification, is catalyzed by thyroid peroxidase (TPO) which then catalyzes a second coupling reaction to create T3 and T4 that is bound to thyroglobulin. This is how the hormones are stored within the colloid until micropinocytosis incorporates the thyroglobin–hormone complex into the cell. Hydrolysis releases the free hormone from the thyroglobulin and T3 and T4 move into circulation.

Thyroid Hormone Synthesis and Release

Thyroglobulin is essential for the synthesis of T3 and T4 in that it serves as a matrix for the synthesis and storage of the hormone as well as

for the recycling of iodide. Thyroglobulin is a glycoprotein dimer produced within the follicular cells and is incorporated into vesicles that migrate to the apical cell membrane. On the apical membrane iodine is coupled to select tyrosyl residues on the thyroglobulin protein. This iodination reaction is referred to as organification and is catalyzed by enzyme thyroperoxidase (TPO), a glycoprotein with a prosthetic heme group that is regulated by TSH [74, 76]. The product of this organification reaction is thyroglobulin with monoiodotyrosine (MIT) or diiodotyrosine (DIT) residues. A second coupling reaction occurs via TPO, with MIT and DIT condensing to form T3 or the inactive hormone rT3. Two molecules of DIT condense to form T4. The process of organification is not random and normally results in 6 MIT, 4 DIT with 2 molecules of T4 and 0.2 of T3 for each thyroglobulin protein. This ratio of T4 to T3 is consistent when iodine intake is sufficient but does vary if there is a significant deficiency or excess of iodine [74]. The iodinated thyroglobulin is then stored as colloid in the follicular lumen (Fig. 1.4). Mobilization of stored thyroid hormone begins with the uptake of thyroglobulin via micropinocytosis and transport into the thyroid cell. The thyroglobulin containing vesicles then fuse with lysosomes which can break down the thyroglobulin and release the final hormonal products T3 and T4. The iodotyrosines (MIT and DIT) are recycled with the iodide and released into the cell via the dehalogenase enzyme to rejoin the iodide cycle. Thyroglobulin itself is also recycled although small amounts are released into the circulation and this can be detected with immunoassay procedures [74, 76]. Overall the ratio of hormones released into serum is similar to that stored within the colloid with the T4 level approximately 10 times that of T3.

Peripheral Transport of Thyroid Hormone

Once released into circulation the vast majority of thyroid hormone is bound to one of three proteins, thyroxine binding globulin (TBG), transthyretin or albumin [77]. Overall the free fraction of thyroid hormone in plasma is small at only 0.03% of T4 and 0.3% of T3. The higher fraction of bound T4 accounts for the longer half-life of T4 at 7 days as opposed to T3 at approximately 12 h. The single most important plasma carrier of thyroid hormone is TBG as it accounts for more than 75% of the thyroid hormone in the blood. This glycoprotein binds a single thyroid hormone molecule and has a half-life of approximately 5 days which helps to maintain constant plasma levels. TBG has a higher affinity for T4 than for T3 and the levels of TBG vary with age and sex. TBG levels are highest in neonates and decline through puberty to reach a relatively stable level during adult life. Transthyretin and albumin both have lower affinities for thyroid hormone and thus make up only a small amount of the binding capacity for thyroid hormone. T3 and T4 may freely dissociate with all of the binding proteins and diffuse directly into cells through the plasma membrane, or bind to membrane receptors that transport the hormone. This combination of high levels of hormone with low affinity of binding to carrier proteins means that there is a stable supply of thyroid hormone at all times despite variations in hormone secretion or metabolism [78].

A number of inherited and acquired abnormalities in thyroid binding proteins have been described with varying clinical phenotypes [2]. Increased total T4 and T3 binding can be due to inherited mutations that overexpress TBG. In addition pregnancy and certain medications including selective estrogens and chemotherapeutic agents can increase thyroid hormone binding to carrier proteins. One inherited condition, familial dysalbuminemic hyperthyroxinemia, has significantly increased levels of bound T4 due to a mutation that increases the affinity of T4-albumin binding but T3 levels are unchanged in this syndrome. There is also a wide range of inherited and acquired conditions that can contribute to lower levels of total T3 and T4 including TBG and albumin mutations as well as liver disease. Altered T3 and T4 levels can also be seen in Hashimoto's thyroiditis and Grave's disease. However, regardless of the mutation or change in the relative T3 and T4 hormone concentrations, the free hormone concentrations always remain normal if the thyroid gland is working properly. Thus an altered binding affinity for hormone seems to have minimal clinical sequlae.

Thyroid Hormone Metabolism and Action on Target Cells

The mechanism of thyroid hormone action was revealed by Tata et al. in the 1960s, through changes in RNA transcription and protein synthesis [79]. It is now understood that the action of thyroid hormone on target cells is tissue specific and regulated through membrane transporter and intracellular enzymatic activity [80–83]. Firstly, thyroid hormone uptake into cells is controlled by unique hormone receptors on the plasma membrane of different cells [84]. Only recently have these transporters been characterized at the molecular level and they have been categorized into two groups as organic anion or amino acid transporters. Some transporters are found in a single tissue while others have a wide tissue distribution. The varying ability to uptake and utilize plasma levels of thyroid hormone represents the first mechanism controlling the effects of thyroid hormone on target cells. The second level of control is via a class of enzymes known as the iodothyronine deiodinases which can control the intracellular levels of T3 and T4 [81–85]. These enzymes, known as D1, D2 or D3 (or Type I, II or III, respectively) are integral membrane proteins that control the relative proportion of T3, T4 and rT3 within the cell and thus influence changes in thyroid hormone action. These three enzymes can activate or inactivate thyroid hormone depending on whether they act on the phenolic or tyrosil rings of the iodothyronines, respectively. Shown in Fig. 1.5 is a schematic diagram of some of the pathways for the conversion of prohormone T4 to T3 and its action on the nuclear receptors. D1 is a kinetically inefficient enzyme that is known to inactivate or activate T4 on an equimolar basis. D2 is the principle enzyme responsible for conversion of T4 to T3. D3 inactivates T3 by converting it to T2 as well as converting T4 to rT3. While it is possible that cells may have all three of these enzymes, only one is typically expressed at a given time and some tissues may express none. D1 is the most common with a presence in most tissues with its highest levels in the liver, kidney and thyroid [2, 80]. D2 is found mostly within the pituitary gland and the brain and D3 is found primarily in placenta, brain and skin. In fact it is the peripheral deiodination of T4, and not thyroid production, which accounts for >80% of T3 in the plasma. Recently it has been revealed that changes in iodothyronine deiodinase activity are important in critical illness [86–88]. Patients with severe acute or chronic metabolic stress, such as in surgery or starvation, may exhibit low normal T4 and undetectable levels of T3. Known as low T3 syndrome, it appears that deiodinase D1 activity is impaired and D3 activity is increased causing a net decrease in T3 and thus slowing metabolic rates in target cells. This may represent an adaptive response to severe stress.

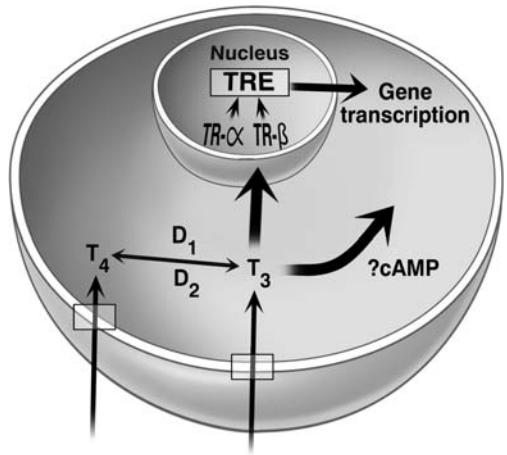

Fig. 1.5. Thyroid hormone action is mediated by the T3 and T4 transport into the cell by the membrane transporters □. Once in the cell the iodothyronine deiodinases D1 and D2 can interconvert the hormone forms to control intracellular levels. D1 promotes equimolar conversion of T4 to T3 or rT3. D2 accounts for the majority of the conversion of T4 to T3. T3 binding to thyroid hormone nuclear receptors (TR), of which there are alpha or beta isoforms, then allows TR coupling to DNA-binding-domains known as thyroid hormone response elements (TRE) that alter gene transcription within the cell. Nongenomic actions of thyroid hormone may be mediated via cAMP. Not shown are the D3 class of enzymes that can convert T4 to rT3 and T3 to T2.

The final step in thyroid hormone signaling is the binding of T3 to nuclear receptors (Fig. 1.5). Thyroid nuclear receptors (TR) then couple to thyroid response elements (TRE) that are located in the promoters of target genes [81]. These promoters may enhance, or repress, the transcription of certain proteins thus altering the function of the target cell. The thyroid hormone nuclear receptors have highly conserved

hormone and DNA binding domains and are part of a superfamily of nuclear hormone receptors that include the steroid and vitamin D receptors. There are different isoforms of this nuclear receptor, TR-α and TR-β with genes located on chromosome 17 and 3, respectively. It is the differential splicing of these genes that lead to the TR-α and TR-β isoforms. Both isoforms of the nuclear receptor have an equal affinity for T3 but the expression of each isoform is tissue specific [80]. Thyroid nuclear receptors are unique among the steroid receptor class in that when it is unbound, it remains active and can bind the TRE and thus provide a level of basal repression of genes downstream. Thus in hypothyroidism the relative decrease in hormone may repress expression of certain genes as opposed to simply being inactive and not positively regulating transcription [80–83]. It is the net effect of thyroid hormone on the products of transcription that mediates its clinical effects. For example thyroid hormones may affect cardiac contractility by altering the relative proportions of the various myosin heavy chains in cardiac muscle [64, 89]. It is important to note however that there may also be non-genomic effects of T3 and T4, via adenylate cyclase (see Fig. 1.5) and mitochondrial activity may be directly regulated by thyroid hormone as well. However, these alternative signaling pathways are not well understood.

Regulation of Thyroid Hormone Production

Levels of circulating thyroid hormone are determined by three different mechanisms of control [64, 80, 90]. The most important factor is the stimulation of hormone synthesis within the thyroid gland via thyrotropin (TSH). TSH is the end-product of the hypothalamus-pituitary-thyroid axis integrating neural and hormonal signals to moderate the demand for thyroid hormone under conditions of illness, starvation or cold. This control cycle begins with TRH which is produced in the para-ventricular nucleus of the hypothalamus. The TRH is released into the hypothalamus-pituitary portal circulation which activates receptors on the thyrotroph cells of the anterior pituitary to synthesize and release TSH. TSH production by the thyrotrophs is typically pulsatile with peaks in the late evening and early morning. TSH release into circulation then stimulates the TFC via TSH membrane receptors on the basal surface of the thyroid cell. Binding of TSH to its receptor then activates adenylyl cyclase and sets off a cascade effect which moderates every aspect of thyroid hormone synthesis and release. Persistently increased levels of TSH lead to gland hypertrophy while decreased levels will allow the gland to atrophy. The hypothalamic-pituitary-thyroid axis is subject to a negative feedback loop where TRH and TSH secretion are decreased by progressively increasing levels of T3 and T4. Thyroid hormone production within the gland is also regulated by iodine availability. Thyroid hormone synthesis can be increased with progressive increases in serum iodide concentration. The system does reach a cutoff where increasing levels of iodide actually shut down hormone synthesis. Reduction of intracellular levels of iodide by reduced activity of the NI symporter allow adaptation of the cell to the new plasma iodine levels and eventually hormone synthesis resumes (Wolff-Chaikoff effect, see previous) [69]. The third aspect regulating thyroid hormone levels is within the extrathyroidal tissues. The transporter mediated uptake of thyroid hormone and its conversion to inactive and active forms within the cell via deiodinases all impact the final action of thyroid hormone in different tissues. Additional factors that may affect hormone synthesis include endogenous or exogenous sources of catecholamines or steroids as well as hCG [64].

Calcitonin Physiology

Calcitonin is most commonly known as one of the triad of compounds, including vitamin D and PTH, that regulate calcium levels in the serum as part of an equilibrium between dietary uptake, urinary excretion, and bone deposition [64, 91]. The hormone itself is a part of a family of related molecules called the calcitonin gene-related peptides (CGRP) in which all sequences contain 32 amino acids with a carboxy terminus proline and a disulfide bridge between residues 1 and 7. Under normal conditions the basal secretion of calcitonin is low. In response to elevated levels of serum calcium, C cells will release calcitonin which acts to reduce osteoclast-mediated bone resorption. This

mode of action is perhaps most useful physiologically in times of stress such as pregnancy or early growth when bone remodeling and calcium release must be tightly controlled [91]. Disruption of bone resorption has also made calcitonin a useful treatment in bone disorders including Paget's disease, osteoporosis, and hypercalcemia secondary to malignancy. However excess levels of endogenous calcitonin, such as with medullary cancer does not cause hypocalcemia. Conversely, loss of C-cell mass by surgical removal of the thyroid also does not appear to disrupt calcium homeostasis. The clinical value of calcitonin is as a marker of disease burden in medullary thyroid carcinoma, and it can be measured with or without calcium and pentagastrin stimuli [91–93].

Interestingly, calcitonin receptors are expressed in many cell types and tissues. The central nervous system (CNS) and gastrointestinal sites are also noted to be able to produce calcitonin where the production is not mediated by calcium levels. Extrathyroidal calcitonin has been proposed to be important for a number of different biological roles including tissue morphogenesis and CNS function. This suggests that calcitonin may have roles other than calcium homeostasis [91].

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2

The Assessment of Thyroid Nodules

Klaus-Martin Schulte

Introduction

The assessment of a thyroid nodule serves several purposes. The patient may experience symptoms from a functional or sizable lesion, or may be at risk of cancer. A thorough history and blood test for TSH, eventually combined with a technetium (Tc) scan, will promptly identify a hyperfunctioning nodule. Symptoms related to the size of a nodule are usually indicated by the patient, and may be crucial in the treatment-making process.

Determining the risk of cancer in a nodule can be a more difficult concept, and the approach involves medical, rational, economic, and cultural considerations. It should be remembered that in dealing with a thyroid nodule, the evidence with regard to outcome, including the prevention of death, and morbidity, from thyroid cancer, is sparse. The natural course of a microcancer or small cancer is not known. They are both frequent findings in postmortem examinations that seem to have caused no morbidity to those who died from natural or other causes. Therefore neither common sense nor evidence supports the assumption that the health of a population or of an individual benefits from an overly aggressive approach to early or small cancers.

For example; in the commonest cancer, papillary thyroid cancer (PTC), there is no evidence that treatment in the earliest stage offers a significant benefit compared with treatment at a slightly later point, when the increase in size of a suspicious nodule has provided evidence that the lesion is dynamically growing. In other words, while the patient may have a risk of cancer, indeed even in the presence of cancer, it is important to avoid causing undue fear to patients, and harm from invasive or unnecessary investigations. The appropriate timing of the assessment for a suspect follicular thyroid cancer (FTC) is equally unclear but is complicated by the fact that undue delay may lead to a scenario where distant metastases have become established from early haematogenous spread. For the less common medullary thyroid cancer (MTC) there is overwhelming evidence that early detection and treatment results in an improved outcome. For anaplastic thyroid cancer (ATC) only early treatment provides a chance of survival.

Based on the enormous variety of biological behaviors and clinical significance of the different forms of thyroid cancer we should question, what we hope to achieve, in assessing a thyroid nodule. Do we want to exclude all risk of cancer? (i.e., histologically classify every lesion).Or do we want to reduce the actual risks of cancer by detecting and treating those cancers, which have a likely or proven propensity to damage the patient? These questions are of both academic, and more importantly, practical relevance. The attempt to exclude all risk of cancer would require an algorithm that enables the fail-safe

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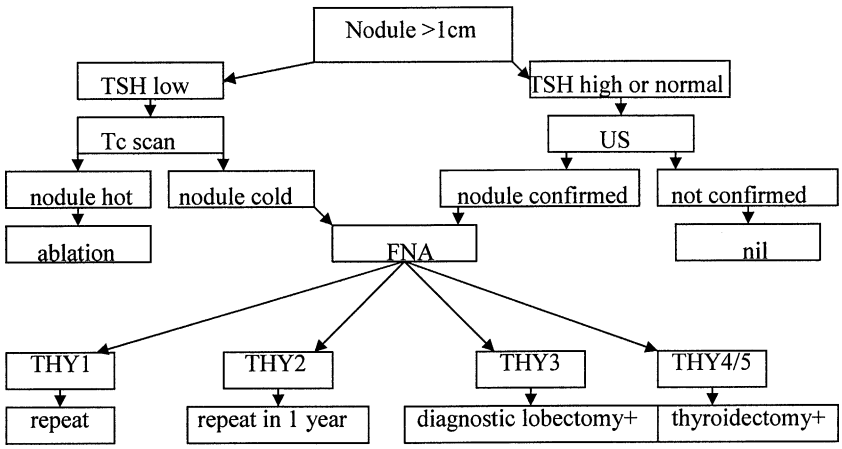

Fig. 2.1. Algorithm for oligosymptomatic and slow-growing solitary or dominant nodules >1 cm.

work-up of every lesion, in a given short time period. The key questions relating to the malignant risk of a thyroid nodule are:

- Do we need to work up every nodule, or target a subgroup?
- To what degree of certainty do we need to exclude malignancy?
- What is the timeline for coming to a definitive diagnosis?

Neither of these key questions can be answered with certainty based on current data, and much of the matter is one of opinion. This should be kept in mind when guidelines and recommendations are read and interpreted. It is a matter of concern that recommendations are not infrequently considered absolute whilst their evidence base is recognizably poor.

Whilst the question of which nodules need to be targeted, is subject to debate, there are many indications that narrow timelines for arriving at a diagnosis are unlikely to benefit the majority of patients, whilst may be vital for some. There is little evidence of clinical benefit for the approach chosen by a number of policy makers and by entire health systems such as the National Health System of England, where the "Improvement of Outcome Guidelines" prescribes narrow timelines for any "suspicious" lesion. These guidelines administer a complex and highly prescriptive referral and deadline system, regardless of the type of cancer and our understanding of tumor biology and its clinical impact. The physician-led attempt to reduce the actual risks of cancer should take a more considered approach and target those lesions with an adverse clinical potential (Fig. 2.1). Growing functional or symptomatic lesions, those with loco-regional or distant metastasis and those of dangerous nature, such as medullary and anaplastic cancer and lymphoma, need to be assessed with urgency and sometimes immediate treatment, whilst those of an obviously less-aggressive nature need a thorough though more delicate approach.

The Rapidly Growing Nodule

The rapidly growing thyroid nodule can rarely be life threatening. These are almost always malignant unless they have grown within minutes or hours, in which case they are usually due to haemorrhage into a cyst. Rapid fluctuant growth of a neck nodule can also relate to sepsis within the oropharyngeal cavity with abscess formation. Clinical examination and inflammatory parameters will rapidly clarify this. Rapid growth of a solid thyroid mass within days or weeks almost always corresponds to ATC or lymphoma. In both conditions the diagnostic work-up needs to be performed with urgency (Fig. 2.2). Complex imaging with CT or MRI scans is of secondary importance and may be postponed for hours or days. The vital first step is to obtain a core needle biopsy (rather than a fine needle aspiration) with urgent processing.

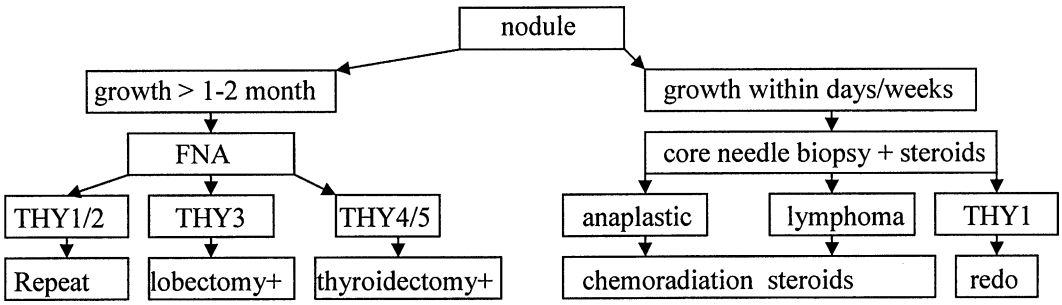

Fig. 2.2. Algorithm for symptomatic and fast-growing nodules.

It is crucial that the receiving pathologist is made aware of the urgency and the clinical differential diagnosis. Given the infiltrative nature of these tumors it may be advantageous to perform an ultrasound (US)-guided biopsy. Lack of availability of such technique must not delay diagnosis, however, and one should then proceed to an immediate palpation-guided biopsy. In our experience there are no reliable parameters to differentiate between ATC and lymphoma on clinical grounds. The course of patients with fulminating lymphoma of the neck can be dramatically changed with intravenous high-dose steroid therapy, which can produce effects within hours, and has few relevant side effects. In this scenario any demands for an urgent tracheostomy should be countered with calm. Such an undertaking is surgically hazardous and may obstruct rational pathways of local external beam radiation. The sequence of action for these nodules is clinical assessment, core needle biopsy with rapid processing of samples, ad hoc start of high-dose intravenous steroid therapy and only then further assessment of the extent of disease followed by specific therapy.

Definition of a Thyroid Nodule

A thyroid nodule is a distinct lesion within the thyroid gland. It may be palpated and/or defined by US. Not all nodules found by palpation actually relate to discrete nodules as defined by US. Not all nodules found by US are palpable since they may be either too small, inaccessible, or of similar consistency to the surrounding tissue. Impalpable nodules have the same risk of malignancy as palpable nodules of the same size [1].

History and Clinical Examination

In patients presenting with local symptoms or a relevant family history, the mainstay of initial diagnosis in any thyroid nodule is history taking and clinical examination (Table 2.1). A nodule must be considered with a high index of suspicion when it is

- fast growing;
- associated with voice change or stridor;
- seen in a patient with a family history of thyroid cancer;
- appears before the age of 14 years;
- appears after prior radiation or exposure to radioactive fallout;
- in a patient with flushing ;
- firm or immobile;
- associated with lymph node swelling in the neck;
- associated with palpable tumor elsewhere.

Nodule Size and Morphology

Size is the most intuitive of all criteria used to evaluate whether a thyroid nodule requires further work-up (Fig. 2.1). It is however amongst the most disputed [2]. Even a small thyroid cancer with a diameter of less than a centimetre can be associated with loco-regional and distant metastases. On the other hand, small thyroid cancers, called microcancers, have been reported at autopsy in around one third of the population who died from unrelated causes. This leaves us with the questions: 1. Which patients should have further investigations once a small thyroid

Table 2.1. Clinical history and examination

History		
Symptoms	Local	speed of growth, pain, swallowing difficulties, voice change, time course
	General	hypo-/hyperthyroidism, B-symptoms, lymphadenopathy, eye problems, vasculitis, gastrointestinal symptoms, bone pain, palpitation, high blood pressure, flushing, diarrhoea, skeletal symptoms
Family	Benign	Graves' disease or chronic thyroiditis, hypertension, pheochromocytoma, calcium excess
	Malignant	thyroid cancer, bowel cancer, other cancer, MEN
Inducing factors	General	country of origin, iodine supply, infectious conditions
	Individual	external beam radiation of local or neighbouring regions, whole whole-body radiation, exposure to radioactive fallout before age 14, work in poorly controlled areas with radiation
Physical examination		
Thyroid	Nodule	size, side, site, consistency, mobility, tenderness
	Other thyroid	other nodules, consistency of thyroid tissue, vibrancy,
Neck	Airway	voice quality, tracheal shift, stridor, positional airway obstruction
	Soft tissues	thyroid in upper thoracic aperture, central or lateral lymphadenopathy, inducibility of swallowing symptoms
General		eyes, signs of hyper/hypothyroidism, palpable masses, lymphadenopathy , dysmorphic findings

nodule is discovered? 2. How do we define "small"? A look at some published guidelines provides us with quite varied answers:

The American Thyroid Association (ATA) Thyroid Guidelines task force recommends that only nodules >1 cm diameter merit further work-up, unless there are specific suspicious features, such as a positive family history for thyroid cancer, history of radiation exposure, or suspicious US features [3]. The British Thyroid Association guidelines for thyroid cancer do not address the issue [4]. The American Association of Clinical Endocrinologists (AACE) guidelines state "an arbitrary diameter cut-off of 10 or 15 mm for cancer risk is not justified" [5]. The American Society of Radiologists in Ultrasound provides us with a consensus that only nodules >2 cm should routinely undergo fine needle aspiration (FNA) [6]. This chapter does not attempt to provide a valid answer. There is no conclusive evidence for any of these positions. In practical terms a cutoff is needed, and this could well vary with multiple factors. A nodule <1 cm in a young patient with a family history of thyroid cancer should trigger an in-depth investigation, whilst a 2-cm nodule may perhaps be disregarded in the 80-year old with multiple comorbidities effectively limiting life expectation. Highly expensive imaging and work-up of all sub-centimetre nodules may be "affordable" for some societies, but the detection of malignancy is low and the cost high in terms of patient worry and morbidity. Size remains the most obvious criterion from clinical examination, but the clinical and to a certain degree the social and economic circumstances should also be taken into account.

A frequent and difficult problem is the assessment of several nodules in the setting of multinodular goiter. Under such conditions FNA may initially not target the relevant nodule because the choice is made on size criteria. Equally, the relevant nodule may be targeted, but missed due to insufficiencies of the approach. Furthermore multiple needle approaches may scare the patient and may prove time-consuming for the clinician. The problem is often dismissed, because no adequate resolution can be achieved or the patient is forwarded for a total thyroidectomy with the need for lifelong thyroid hormone replacement therapy and its surveillance. Since goiter is an extraordinarily frequent finding, specifically in areas of suboptimal iodine intake, the problem of multiple thyroid nodules of indeterminate nature is one of the most commonly encountered diagnostic problems. FNA is unable to

differentiate benign and malignant conditions in follicular neoplasm. The likelihood of finding thyroid cancer following an FNA suggestive of a follicular neoplasm, Hurthle cell lesion or indeterminate result, decreases with the increasing number of other thyroid nodules. In one large study the risk of malignancy in the target lesion was twice as high when the lesion was solitary as compared with those where 1–3 further nodules were present [7]. This author believes that individual nodules in a multinodular goiter should be specifically assessed if they are dominant, i.e., much larger or of different structure than the surrounding tissue and nodules, or if they show significant growth.

Thyroid Function

Hyperthyroidism (see also Chapter 6) in conjunction with a palpable or impalpable nodule is a frequent and functionally important condition, however, the thyroid nodule requires assessment out with the functional endocrine aspects. The guidelines provided by the British Thyroid Association shifts all patients with an abnormal TSH into routine endocrine referral pathways, whilst it recommends a speedier work-up through cancer-related pathways for many other scenarios [4]. This statement may be based on the long-held belief that thyroid cancer in toxic nodules is a rare event. However, this misses the point that the thyroids of many patients with hyperthyroidism harbor nodules, which are not related to excess hormone production and may be either nonfunctional or normally functioning. These nodules do not fall into a low-risk category because they occur in a thyroid which also produces excess hormone. They merit the same scrutiny as proposed for nodules in the euthyroid patient of the same size. A recent retrospective study on 2,449 patients with hyperthyroidism has found an astonishingly high rate of thyroid cancer [8]. Thyroid cancer was found in 6.5% of Graves' disease with one or more nodules, in 4.4% of those with a solitary toxic nodule and in 3.9% of those with a multinodular toxic goiter. Lymph node involvement was seen twice as frequently in the Graves group (56%). Based on these figures US-guided (USG)-FNA of all cold nodules in hyperthyroid patients with nodules has to be recommended.

Another useful though not fully explained finding, is that serum concentration of thyroid-stimulating hormone (TSH) also helps to determine the malignant risk of nodular lesions [9]. As a rule, the risk of cancer significantly and continuously increases with rising TSH levels even within the normal range of TSH. The risk of cancer was several-fold higher in patients with a TSH above the normal range compared with those with a low-normal TSH. Similar results were reported in a study which assessed the likelihood of cancer in 843 patients undergoing thyroid surgery [10]. Here again, the group with a high-normal TSH had a threefold increased risk of cancer compared with the group with a low-normal TSH.

In summary, an abnormal TSH increases the likelihood of finding a cancer in a patient with a thyroid nodule. Such patients should be viewed with a higher index of suspicion.

Fine Needle Aspiration

FNA is today the mainstay in the assessment of a thyroid nodule. It is a simple, fast, and inexpensive procedure, which obtains cellular material for cytological analysis. FNA is recommended as first-line test for almost all nontoxic nodular thyroid changes above a certain size and relevant guidelines coincide with this point.

Recently a series of 2,587 consecutive patients undergoing thyroid US found nodules larger than 1 cm in 14%. USG FNA was performed [11]. Cytology had a positive predictive value (PPV) of 97% and a negative predictive value (NPV) of 99.7%. The cancer rate in those referred for surgery was 56%, which is much higher than typical yields, which tend to stagnate around 20%. In general, the sensitivity and specificity of an FNA to predict malignancy is thought to be 80–95%.

There is enough study data to indicate that dismissal of a thyroid nodule based on the fact that it is impalpable may be inappropriate. A study of 494 consecutive cases [12] with impalpable nodules revealed thyroid malignancy in ~9% of solitary nodules, and in ~6% of multinodular goiters. Cancer prevalence was similar for nodules greater than, or smaller than, 10 mm (9.1 vs 7.0%).

Whilst there is consensus on the use of FNA for the primary assessment of thyroid nodules,

there is no agreed algorithm of what to do with those patients in whom one FNA is benign. There is considerable evidence that a repeat FNA would improve cancer detection. Overall, performance of a single-repeat FNA increased the sensitivity for malignancy from 81.7 to 90.4% and decreased the false-negative rate from 17.1 to 11.4%. With more than one repeat FNA, there was no further improvement in performance [13]. Repeat FNAs are most to be beneficial where a lack of experience or equipment leads to inadequacies in sampling or subsequent cytological assessment. The above quoted study delineates results at the upper range of FNA-proficiency. In clinical practice, repeated FNA during long-term follow-up may be needed to detect thyroid cancer in a suspicious nodule [14, 15].

Freehand and USG FNA

A lot has been said and written about the choice between USG and freehand FNA. Most studies demonstrate a significantly higher yield of diagnostic aspirates if US is used to guide the procedure. Danese [16] compared the diagnostic accuracy of palpation-guided, i.e., PG-FNA versus, USG-FNA on a large sample population of 9,683 patients. About 4,986 patients were investigated by PG-FNA and 4,697 underwent USG-FNA leading to a valid cytological diagnosis in 85.9 and 91.5%, respectively with a diagnosis of thyroid cancer in 1.6 and 2.1%, respectively. Specimens were cytologically inadequate in 433 PG-FNAs (8.7%) but only in 167 USG-FNA cases (3.5%). False-negative results occurred in seven PG-FNA nodules (2.3%) but only in three USG-FNA cases (1%). Sensitivity, specificity, and global diagnostic accuracy of PG-FNA compared with USG-FNA were 91.8 versus 97.1%, 68.8 versus 70.9%, and 72.6 versus 75.9%, respectively.

Generally, inadequacy rates are around 5–20%, and it is well documented that the experience of the performer seriously impacts on adequacy rates with up to tenfold difference in outcomes. However, conclusions should be drawn with common sense. Larger, well-palpable, easily located nodules can be well targeted with PG-FNA, whilst small, posterior, hardly palpable or impalpable nodules will require USG -FNA. If these rules are adhered to, it is less the choice of guiding technique, but the presence of a cytologist at the sampling site, which determines the adequacy rate of FNAs. If smears are reviewed immediately, inadequate samples can be recognized and the test repeated [17]. The largest group of inadequate samples was obtained from cystic lesions, and of course these were best recognized and targeted using US.

The results of FNA are of varying quality depending on the type of lesion subjected to the test. It is worth reviewing the findings from more than two decades at the Mayo clinic. When cytology showed a follicular neoplasm the final histology was cancer in 15% (83/561); Hurthle cell neoplasm 14% (77/548); PTC 65% (318/489); with an overall rate of cancer of 29% (478/1,598) [18].

Although FNA is generally considered a very safe procedure, bleeding into cysts or even massive intrathyroid haemorrhage with acute airway obstruction can result from the procedure. It is important for the surgeon to know that FNA may result in temporary and rarely in permanent vocal cord palsy. A study on 10,974 patients undergoing FNA revealed four symptomatic cases of temporary recurrent nerve palsy amounting to about 0.04%. [19] However, there may be a higher rate of undetected asymptomatic paralyses, which when unmasked by surgery could be wrongly ascribed to the surgical intervention.

Ultrasound in Malignant and Benign Nodules

The yield of US is highly observer-dependent. It requires experience, time, and dedication as well as good equipment. The latter has recently become much more accessible in form of handheld devices coupled to labtop computers.

The main role of US in is the identification of all thyroid nodules, their characterization (Fig. 2.3), and relative position to vascular and other structures. It has become clear that malignancy is as frequently found in impalpable, as in palpable lesions. A survey of the literature shows that the majority of reported thyroid cancers are small. US is the single most important gateway to discovery of such lesions. Screening US of 16,352 patients in one center

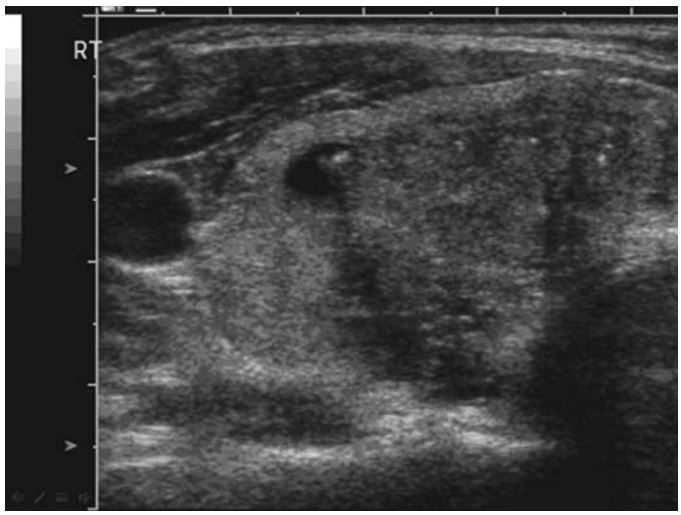

Fig. 2.3. Ultrasound of PTC with calcifications and irregular margins (courtesy of Dr PS Sidhu, Radiology, King's College Hospital, London).

[20] discovered 1,325 impalpable nodules. They were subjected to FNA, which revealed 150 malignant nodules. Features suggestive of malignant change were marked hypoechogenicity, an irregular shape, a taller-than-wide shape, a well-defined spiculated margin, absence of hypoechoic halo around the nodule, microcalcification, and an entirely solid nature ($p < .05$). A size cutoff of 1 cm in the longest diameter was not significant ($p = .184$), however, extracapsular invasion ($p = .024$) and lymph node metastasis (p = .019) were observed more frequently in carcinomas >1 cm (73 and 42%, respectively) than in microcarcinomas (38 and 13%). Microcalcifications are one of the most specific US findings of a thyroid malignancy [21]. In performing US it is important to examine the central and lateral compartments with utmost care and record the level-specific location of any enlarged lymph nodes. These may be infrequent findings, but their presence is important in the diagnosis of cancer as well as highly informative for the surgeon in planning surgery. Local invasion of adjacent structures is infrequent, but when detected is valuable information. The number, size, and interval growth of nodules are nonspecific. The interpretation of diffusely infiltrative thyroid carcinomas and multifocal carcinomas can be difficult based on US appearances. However, US robustly describes the solid, cystic, or mixed nature of the lesion. As such, US is a powerful tool to exclude a huge group of nodules from further examination and work-up. Even in patients with an USG-FNA, the major reason for a missed diagnosis of PTC is inadequate tumor sampling due to the heterogeneity of the nodule [22].

CT and MRI

Computed tomography (CT) has no role in the routine assessment of thyroid nodules.

Recent studies have reported on the use of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Only small series are available so far. One has shown that the sensitivity and the NPV of DCE-MRI is superior to that of USG-FNA [23]. The data basis is not solid enough to give recommendations for a more widespread use of this potentially helpful but expensive screening method.

Nuclear Medicine

Nuclear medicine techniques remain paramount in the diagnosis and treatment of thyroid cancer. Their role in the work-up for thyroid nodules is much more limited today. Tc

scanning remains a first-line test in patients with a low or suppressed TSH, in whom the scan differentiates between focal and generally increased thyroid uptake or strongly contributes to the diagnosis of thyroiditis, when uptake is low.

Tc-99m scanning has long been used to evaluate the malignant potential of thyroid nodules. However, there is large variability in its use and recommendations around its use. These are related to the fact that there is relatively little hard data to indicate that it is a sensitive and specific test. The role of Tc scanning of the thyroid changed during the 1990s, and it is now considered a second-line tool in the evaluation of thyroid nodules and recommended only after thyroid function tests and FNA [24]. In clinical practice it may be used to help stratify the risk of malignancy in a nodule, when an FNA has failed. The assumption is that hot or warm nodules rarely harbor cancer, and that cold nodules alone would need more aggressive, e.g., surgical treatment. Malignancy is not less likely even in hyperthyroid patients. It is of note, however, that the largest retrospective study on cancer incidence in hyperthyroid patients used "cold nodules" as a trigger for surgical treatment and therefore for clarification with histology. [8]

Tc-99m methoxy isobutylisonitrate (MIBI) can be taken up by thyroid cancer. When used in cold solitary nodules it has a specificity of 95% and a PPV >90%, whilst the sensitivity is around 84%. Larger prospective studies are needed to evaluate the usefulness of such an approach.

A recent smaller study of delayed Tc-Tetrofosmin scintigraphy in the detection of thyroid cancer showed a sensitivity, specificity, PPV, and NPV of 86.6, 97.2, 92.8, and 94.7%, respectively [25]. It remains to be clarified whether such usefulness can be confirmed in larger cohorts and in the more common setting of multinodular goiter.

The Role of Calcitonin Screening

It has long been debated whether Calcitonin should be systematically measured in patients with thyroid nodules. Measurement of serum Calcitonin has a very high sensitivity and specificity for MTC, depending on the cutoff levels (Fig. 2.4).

Those in favor argue that such screening would detect a small but significant number of presymptomatic and hence likely curable MTCs and might detect a very small number of index cases with familial MTC and multiple endocrine neoplasia (MEN). Those against refer to the high cost of the assay and the low yield of the test. A large study published in 2007 obtained a baseline Calcitonin in 5,817 consecutive patients and identified 15 patients with MTC (0.26%) and 7 patients with C-cell hyperplasia (0.13%) [26]. PPV for basal CT levels in the diagnosis of MTC were 23.1% for values ≥20 pg/ml, 100% for values >100 pg/ml, 25% for levels between 50 and 100 pg/ml, and 8.3%

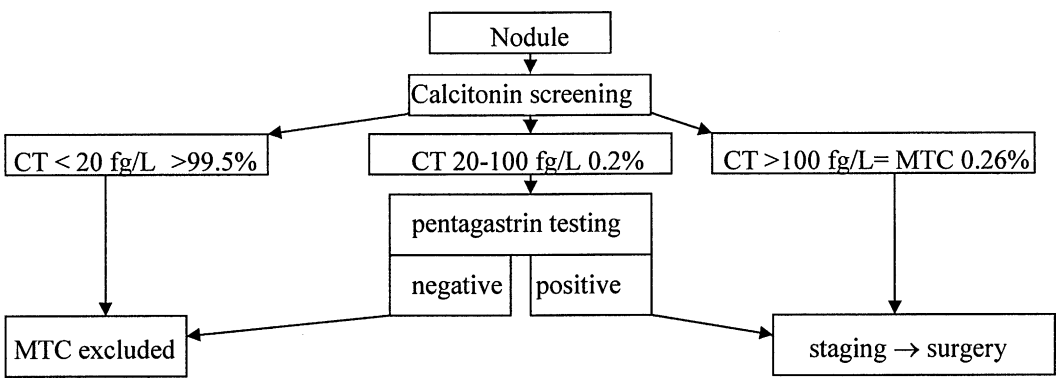

Fig. 2.4 Calcitonin screening for the detection of MTC.

for values between 20 and 50 pg/ml. PPV for the pentagastrin test (>100 pg/ml) was 40%.

Calcitonin screening of thyroid nodules is a highly sensitive test for early diagnosis of MTC, but confirmatory stimulation testing is necessary in most cases to identify a true-positive increase. We feel that exclusion of MTC and associated conditions specifically in the younger age group would lead to a significant reduction in life-years lost due to thyroid cancer in general, since survival rates of MTC are so much poorer than and PTC or FTC. When this endpoint is chosen, it is likely that Calcitonin testing may turn out to be more health-effective and cost-effective than the routine US and FNA of small thyroid nodules.

Thyroid Cancer Gene Expression Profiling and Proteomics

As details on gene expression patterns in thyroid cancers are gathered there is hope for the identification of novel diagnostic biomarkers. While individual studies have proposed hot candidates, none has yet been introduced into routine clinical practice. The reasons for delay include difficulties in achieving reproducible and reliable results from small samples and the lack of sensitivity and specificity of individual markers. A meta-analysis of gene expression-profiling studies has identified a dozen "hot" candidates such as MET, TFF3, SERPINA1, TIMP1, FN1, and TPO, as well as relatively novel or uncharacterized genes [27]. A recent study using differential gene expression has shown that a small set of 19 genes can be used to differentiate benign from malignant follicular neoplasms and other cancers based on FNA material [28]. These results await validation in a prospective clinical trial.

An alternative pathway to gene expression profiling is pattern analysis of proteins by proteomics. This technique faces specific problems in thyroid samples due to the huge fraction of thyroglobulin in specimen. However, prefractionation techniques now allow a much narrower analysis of samples, with clearly definable patterns for nodular versus normal thyroid tissue [29].

2-[^{18}F] fluoro-2-deoxy-D-glucose-Positron Emission Tomography (18)

A number of studies have evaluated the role of 2-[^{18}F] fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) for diagnosis and staging of thyroid cancer. A large survey in 2007 did not identify an established role for PET or PET-CT [30]. High costs, ranging between $1,200 and $2,600, make it an unlikely tool for primary assessment of thyroid nodules. However, some authors propose the use of FDG-PET in thyroid nodules in which FNA has failed to clarify the diagnosis [31]. The sensitivity for detection of malignancy with FDG-PET is high, but the specificity is <40%. The most remarkable feature of FDG-PET is the NPV. In most studies this approaches 100% [32]. Lesions without focal uptake are highly unlikely to be malignant. The presence of uptake, however, does not predict malignancy, and is a common feature of follicular lesions of any type [33]. This test, though expensive, could be useful in the minority of patients in whom FNA has repeatedly failed, and surgical risks are high, such as recurrent nodular changes or an increased general morbidity.

Relationship of Thyroid Nodules with Other Conditions, e.g., Systemic Cancer, Lymphoma, or Septic Diseases

Thyroid abscess is a rare pathology underlying a thyroid nodule. Today, a diagnostic needle aspiration may not only identify the causative agent, it may also be therapeutic, when followed by appropriate antibiotic therapy. Recent decades have seen a rise in tuberculosis (TB). Thyroid TB remains a rare condition with less than 100 reported cases [34]. The presentation ranges from a single nodule to TB thyroiditis. Diagnosis is achieved by culture of FNA aspirates, followed by conservative management with anti-TB drugs.

Specific Situations

Nodules Presenting in Pregnancy

There is no evidence that thyroid nodules diagnosed during pregnancy behave more aggressively. It is important that thyroid function tests are obtained and pregnancy-related iodine deficiency associated with rise in TSH is ruled out. Work-up is similar to that of the nodule in the general population. US and FNA are safe in pregnancy. Of course nuclear medicine scanning and X-ray exposure are contraindicated. There is hardly ever an indication for invasive diagnostic testing (e.g., by lobectomy) in the first trimester of pregnancy. Lobectomy is reasonably safe in the second trimester, but can, in almost all cases be safely postponed until after delivery and breast-feeding, unless there are convincing features of malignancy. In other cases, a follow-up US during pregnancy may be reassuring for mother and doctor. In general terms alarmism must be avoided and particular care needs to be taken to provide messages in the appropriate context.

Nodules Presenting in Childhood and Adolescence

Thyroid nodules in childhood and adolescence are rare. However, they have an increased risk of being malignant. PTC is the commonest cancer type. MTC in younger children is most commonly found in the context of MEN II, and FMTC. Although there is no firm evidence basis, we would recommend checking a serum Calcitonin in every child with a thyroid nodule. A family history is a clear risk factor for cancer, as is previous neck irradiation, the latter particularly in girls.

Thyroid nodules in children should be treated with a much higher index of suspicion, specifically when they are solitary. In our experience palpation is often a very revealing examination since the neck is amenable to palpation and subcutaneous tissue is mostly thin. The differential diagnosis comprises benign thyroid conditions such as congenital hypothyroidism, thyroid hemiagenesis, thyroglossal duct cyst, simple goiter, cystic lesion, nodular hyperplasia, follicular adenoma, nodular Graves' disease, and Hashimoto thyroiditis, which predisposes to the development of thyroid nodules [35]. Scintigraphy alone or supported by US may help to identify thyroid dysgenesis.

Thyroid Nodules in Secondary Hyperparathyroidism

There is relatively little data on the prevalence of thyroid cancer in patients suffering from end-stage renal failure and secondary hyperparathyroidism (SHPT). One of the largest studies [36] describes simultaneous resection of some part of the thyroid mostly because of nodular disease in 133 (39%) of 339 of patients undergoing surgery for SHPT. PTC was found in eight patients (2.4%) and FTC in one patient. The cancers were all T1 tumors and many were only millimetres in diameter. The clinical relevance of these small incidental tumors is as uncertain as those found in autopsy studies.

The Nodule Detected on Whole-Body 18F-FDG-PET-CT

PET-CT is increasingly used for cancer staging and sometimes for screening. Based on more than 7,000 consecutive patients around 1.1% of such examinations discovered a focal thyroid uptake [37]. Further analysis revealed malignancy in roughly one third of such patients. The majority of lesions where PTCs, while rarely lymphoma or metastases from squamous cell cancer were found [37]. The amount of uptake does not allow a reliable differentiation between benign and malignant conditions in most published series.

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3

Thyroid: Fine-Needle Aspiration Biopsy

Fuju Chang, Ashish Chandra and Amanda Herbert

Introduction

Epidemiological studies suggest that nodular thyroid disease is a common clinical problem, with a prevalence of 3% of the UK and 2–7% of the US populations [1, 2]. Nodules are even more prevalent when the thyroid gland is examined at autopsy or surgery, or when using ultrasonography; over 50% of the thyroids so studied have nodules, which are almost always benign [3, 4]. Only 5% of all thyroid nodules prove to be malignant [3, 4]. Therefore, many of these benign nodules can be followed clinically, treated medically or managed with conservative surgery for symptoms [2, 5, 6].

During the last few decades, thyroid fine-needle aspiration (FNA) biopsy has supplanted other tests and has become the best triage test for the preoperative evaluation of thyroid nodules [7–11]. Consequently, this technique has reduced the number of thyroid operations by about half and has at least doubled the proportion of cancers found at surgery [5, 7–11].

Indication and Goal of Thyroid FNA

The main value of thyroid FNA is in diagnostic triage of patients who need surgery and, more importantly, those for whom surgery may be avoided. In the hands of experienced operators this technique achieves high diagnostic accuracy. Therefore, use of thyroid FNA is recommended for all palpable solitary or dominant nodules, independent of size [12–16].

Traditionally, the main indication for thyroid FNA has been the presence of a solitary nodule. It has been taught that the risk of cancer in a multinodular goiter is much less than that in a solitary nodule. However, recent literature indicates that if a nodule in a multinodular goiter has grown steadily, become distinctly dominant or changed in consistency, its risk of malignancy is the same as that for a solitary nodule [17, 18]. Under these circumstances, FNA investigation is indicated.

In autoimmune thyroid diseases, such as Graves' disease and Hashimoto's thyroiditis, a dominant localized abnormality in the thyroid gland is an indication for FNA [12–16, 19]. FNA biopsy is also required for a diffuse, rapidly growing thyroid enlargement to rule out anaplastic carcinoma or lymphoma, especially in patients over 50 years of age [12, 13, 15].

The evaluation of thyroid nodules in a pregnant woman is the same as for a nonpregnant patient, with the exception that a radionuclide scan is contraindicated [12]. For euthyroid and hypothyroid pregnant women with thyroid nodules, FNA should be performed. For women with suppressed serum TSH levels that persist after the first trimester, FNA may be deferred until after pregnancy when a

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radionuclide scan can be performed to evaluate nodule function.

Thyroid FNA examination is also sensitive and specific in the diagnosis of childhood nodular thyroid disorders [20–22]. Thyroid nodules occur less frequently in children than in adults. However, some studies have shown the frequency of malignancy appears to be higher in children than in adults [20–22].

The FNA should be repeated for cases with inadequate yields following the first attempt, because repeating the aspiration provides an adequate sample in as much as 50–88% of the initially unsatisfactory cases [8]. In addition, recent data strongly support the clinical usefulness of one repeat FNA after an initial benign aspiration. The use of one repeat FNA increases the sensitivity for malignancy from 81.7 to 90.4% and decreases the false-negative rate from 17.1 to 11.4% [23].

Overall, FNA is preferred over thyroid scan or ultrasonography as the initial diagnostic test for thyroid nodules. However, a previous ultrasound may aid the physician performing the aspiration of lesions that are difficult to palpate.

Contraindications and Complications of Thyroid FNA

Because FNA of the thyroid is an invasive procedure, albeit minimally so, complications are possible although extremely rare [9, 11, 24, 25]. Needle puncture may cause slight pain and some skin discoloration at the aspiration site(s). Bleeding complications occur only infrequently as either localized swelling or bruising after the procedure but are usually avoided if firm pressure is applied to the aspiration site. Tracheal injury is manifested by minimal and transient hemoptysis. Needle tract implantation of thyroid carcinoma is extremely rare; it has been poorly documented and is not considered a real problem by most experts [9, 11, 24–27].

Although the use of anticoagulants or salicylates does not preclude FNA, it is recommended that aspirin or other agents that affect coagulation should be discontinued for several days before the procedure [12, 15]. Bleeding is more likely with large needles [24, 25].

Technical Aspects of Thyroid FNA

Selection of Technique

A thyroid nodule can be aspirated manually or under ultrasound (US) guidance. Ultrasound examination of thyroid nodules provides structural information about the location, number, size, and the gross morphology of the nodules. Several studies have attested to its value and have shown that this method can effectively increase the sensitivity and specificity and decrease the nondiagnostic rate as compared with manual thyroid FNA [28, 29]. This is especially true in thyroid lesions that are

- difficult to palpate due to smaller size;
- arising in the posterior aspect of the thyroid;
- nodules associated with diffuse pathological processes such as lymphocytic thyroiditis, and Graves' disease;
- palpable thyroid nodules that are deemed be nondiagnostic on manual FNA due to extensive cystic change or fibrosis. In such cases, US-guided FNA can easily target the solid portion of the nodule to acquire diagnostic material.

When FNAs are taken with ultrasound guidance care must be taken to avoid contaminating the cellular material with gel, which may render the cytology difficult or impossible to interpret accurately.

The initial step of thyroid FNA is localizing the nodule or nodules to be aspirated, which is followed by selection of the needles to be used. Usually a 25- or a 27-gauge needle is preferred [9, 24, 25]. The use of larger needles, 0.7 mm (21 gauge) or more, in most cases results in a rich admixture of peripheral blood, which is a distinct disadvantage for cytological examination. In addition, more pain is caused by the use of large needles. Local anaesthesia is however not necessary.

Regardless of who carries out the procedure, it is important for a second individual, preferably a cytopathologist or cytotechnologist to be present to prepare the slides, assess adequacy of the sample, and retain material if needed for ancillary techniques.

Specimen Procurement

Although both suction and nonsuction techniques have been described for thyroid FNA-biopsy, it is generally recommended that the nonsuction technique with a 25- or a 27-gauge fine needle is used first [9, 24, 25, 30, 31] (Fig. 3.1), as this technique is simple, produces specimens that are less bloody and is particularly effective for aspirating small lesions. However, the conventional suction technique sometimes yields more material than the nonsuction technique and vice versa, so it is unwise to use one technique to the exclusion of the other. If a cyst is encountered during nonsuction FNA, suction with a larger needle attached to a 10- or a 20-ml syringe held by a "pistol-grip" device is recommended, to evacuate as much fluid as feasible. If there is a residual solid area, then a 25- or a 27-gauge needle may be used for nonsuction sampling of this area.

The patient should be told before the procedure that more than one aspirate may be needed to obtain enough material for diagnosis and sometimes for extra tests. During the procedure the patient is asked to keep still and to refrain from swallowing. The needle is gently inserted into the nodule and then moved in and out 5–10 times (Fig. 3.1). Aspirate flows into the needle through capillary action and, as soon as aspirate appears in the hub, the needle is withdrawn and attached to the syringe with air inside to expel the material onto glass slides (Fig. 3.1).

Firm pressure should be applied to the biopsy site for at least 1 min immediately after the needle is withdrawn, and the needle (or needle with a syringe and holder) should be handed without delay to the person preparing the slides. The needle should be turned away from the person receiving it or, preferably, should be placed in a shallow container. The slides should be prepared immediately to avoid clotting or cellular degeneration. As long as there is no significant bleeding, and any repeat aspirates have been taken, an adhesive dressing may be placed on the puncture site(s). The patient is observed for a few minutes and, if there are no problems, the patient is allowed to leave the FNA clinic.

Although it has been suggested that more aspirations will increase the diagnostic rates, the optimal number of aspirations is a matter of debate. It is generally recommended that a minimum of two passes should be taken from various portions of the nodule to decrease sampling error. Most reports indicate that two to

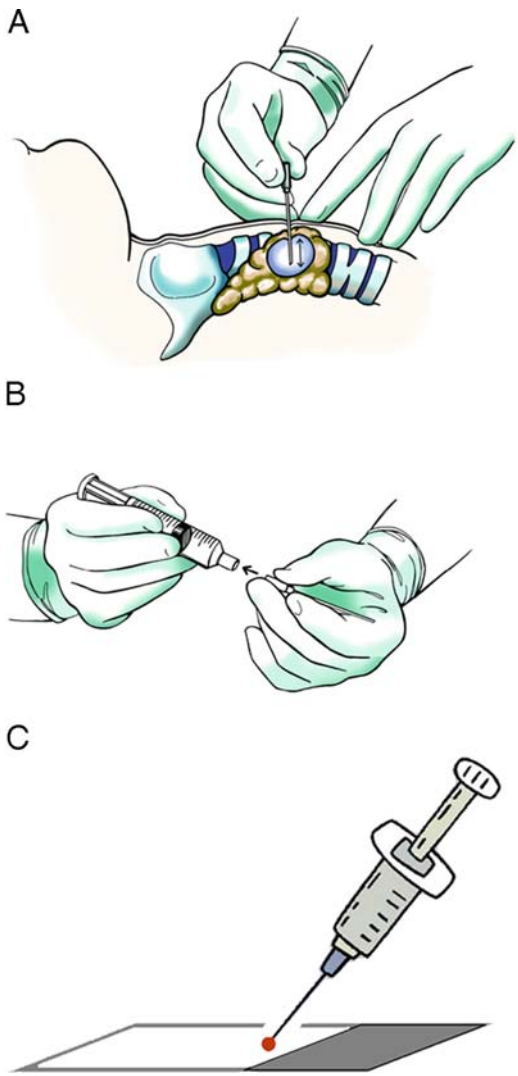

Fig. 3.1. Demonstration of nonsuction FNA of the thyroid (modified from reference [28]). (**A**) The needle is held directly between the thumb and the index finger. The nodule is immobilized with the index and middle fingers of the other hand. The needle is moved back and forth several times within the nodule with a rapid, gentle, stabbing motion. (**B**) After the needle is withdrawn, an air-filled syringe with its plunger already retracted is immediately attached to the needle. (**C**) The needle contents are expelled onto clean glass slides. Thin, evenly spread smears are prepared from the ejected material.

four aspirates per nodule are adequate [9, 24, 25, 30, 31], but, occasionally, as many as six needle punctures may be required.

The on-site evaluation of thyroid specimens with rapid cytology stains could dramatically reduce nondiagnostic rates [32, 33]; however, this may not be available in all clinical settings but should always be recommended, especially where inadequate rates are high. There are a number of advantages to on-site evaluation, which include assessment of adequacy of the specimen, provisional classification of the lesion and triage so that appropriate material may be collected for additional studies such as immunocytochemistry, microbiological analysis, flow cytometry and genetic studies [32, 33].

Specimen Preparation and Staining

Following needle aspiration, the aspirated cells are immediately and gently expelled onto a glass slide. Parallel preparation of alcohol-fixed and air-dried smears from the aspirated material is recommended [9, 24–26]. Wet-fixed smears are usually prepared with a modified Papanicolaou stain, which shows nuclear details such as grooves and inclusions, which are crucial for the diagnosis of papillary carcinoma [24–26]. Air-dried smears are often prepared with the Romanowsky modified methods (Hemacolor, May-Grunwald–Giemsa or Diff-Quik method), which can highlight the background watery colloid and cell architecture (papillary, monolayer sheets, and macro- and microfollicles) and distinguish between cell types (follicular, Hurthle, lymphocytes, and macrophages) [24–26]. The Romanowsky staining method is also one of the best methods available in cytology for immediate evaluation of thyroid FNA specimens [32, 33].

The following issues should be considered when preparing the specimen:

- It is important that a small drop of aspirated material is used for smear preparation because if a large drop of aspirate material is used, a thick smear will be obtained (Fig. 3.2). This will lead to slow drying of the smear and loss of cellular details, making the cytological evaluation difficult.
- It is also important that the material is smeared immediately after being expelled as air-drying of the droplet causes the cells to crush when spread (Fig. 3.2).
- Instead of direct smearing, cytospin preparations should be performed from the liquid contents of cystic thyroid lesions.
- For alcohol fixation, the smears must be placed promptly in 95% alcohol or with a commercial spray fixative, before any air-drying occurs. A delay in fixation will result in air-dried artifactual changes with loss of cellular details.
- Any remaining material can be rinsed in balanced salt solution. The rinses are held in reserve to be used for cytospin, cell block preparation or further ancillary tests at the discretion of the cytopathologist.

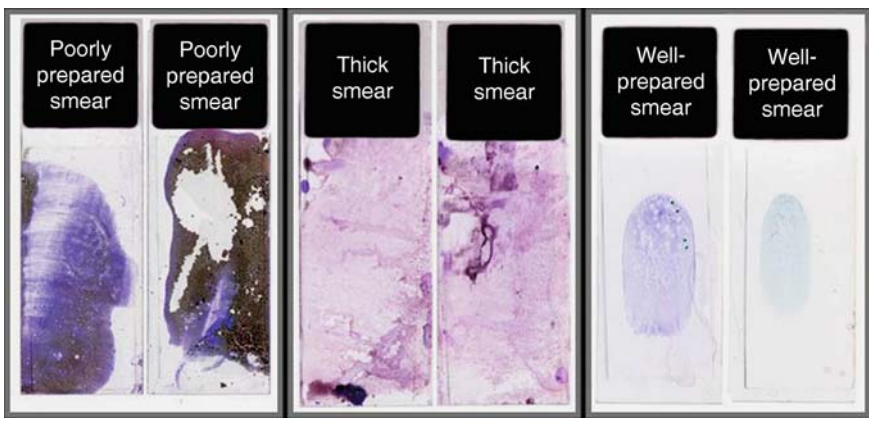

Fig. 3.2. Preparing a direct smear is an art in itself, which should not be left to anyone who is unable to assess the cytology.

- When blood clots or visible tissue fragments are present, they may be gently removed and used for cell block preparation, as needed.
- If the aspirated material is to be used for immunocytochemistry, direct smears can be used; but in most instances it is preferable to make a cell suspension in buffered saline. The cells are then collected by centrifugation to make thrombin-induced cell blocks or cytospin preparations. Cells may also be fixed in formalin for commercial cell block techniques.
- Newer techniques have been developed, for example, liquid-based cytology. This allows lysis of blood and thin layer preparation [34]. However, the cytological appearances with liquid-based cytology are somewhat different to those on conventional smears and further experience of the technique is required. The major disadvantage of thin layer preparations is that the colloid, which is important for diagnosis, may not be fully preserved. Indeed, some studies have suggested that liquid-based thin layer method appears to be not ideal for use in thyroid aspirates [35, 36].

Immunocytochemistry and Other Ancillary Techniques

Immunocytochemistry and Flow Cytometry

Several tumor markers have been shown to be helpful in thyroid pathology [37–39]. Their application to cytology has also been suggested, but there are limitations, as shown by the lack of specificity. Panels of these markers may yield supportive information in the differential diagnosis of thyroid nodules.

Cytokeratin 19 (CK19) is a high-molecular weight cytokeratin that is a sensitive but not a specific marker of papillary carcinoma. It is often diffusely expressed in papillary carcinomas [38, 39], but focal positive staining can also be seen in some follicular lesions, chronic lymphocytic thyroiditis and even in compressed nonneoplastic thyroid tissue around thyroid lesions [38, 39].

HBME-1 (Hector Battifora and mesothelioma 1) is a monoclonal antibody that was initially promoted as a marker of mesothelial cells. In the thyroid, HBME-1 is almost exclusively expressed in malignant neoplasms, including papillary carcinoma, whereas benign lesions are negative [37–39]. HBME-1 is the most specific marker of thyroid malignancy, but it may not be very sensitive because oncocytic lesions are generally negative; also, not all thyroid malignancies are stained by this antibody. HBME-1 positivity is characterized by predominantly membranous staining with variable cytoplasmic staining.

Galectin-3 is a member of the lectin family that has physiologic and pathological functions including growth regulation, development, differentiation and cell–cell adhesion. Galectin-3 has been promoted as a marker of malignancy in thyroid; however, its expression in some cases of multinodular goiter and in thyroiditis limits its application [37, 39].

Immunostaining with thyroperoxidase antibody has been reported to be of value in distinguishing benign and malignant follicular lesions, the former being commonly stained positively while the latter being often stained negatively with this antibody [40].

Immunostaining for thyroid transcription factor-1 (TTF-1), thyroglobulin, and calcitonin may be indispensable to identify the cell type in poorly differentiated neoplasms. These markers are also useful in examining tumors in metastatic sites.

Flow cytometry is a technique that helps greatly in the cytologic evaluation of lymphoid malignancies [41, 42]. By this ancillary technique one can separate lymphoid neoplasms from a reactive processes by establishing clonality. Flow cytometry also helps separate lymphoid malignancies into those of T- or B-cell origin as well as helping to further subclassify the different lymphomas. Immunocytochemistry in conjunction with flow cytometry for lymphoid markers is of great value in the diagnosis of lymphoid infiltration of the thyroid [42]. The technique described above for retaining cell washings in balanced saline allows the option of flow cytometry or immunocytochemistry as indicated by the morphology. A flow chart for processing needle washings and ancillary tests is shown in Fig. 3.3.

DNA and Molecular Techniques

Molecular techniques including microarray analysis and molecular profiling may have significant roles in the future evaluation of thyroid nodules, while providing impetus for further insight into the molecular pathogenesis of both benign and malignant lesions [43, 44]. For

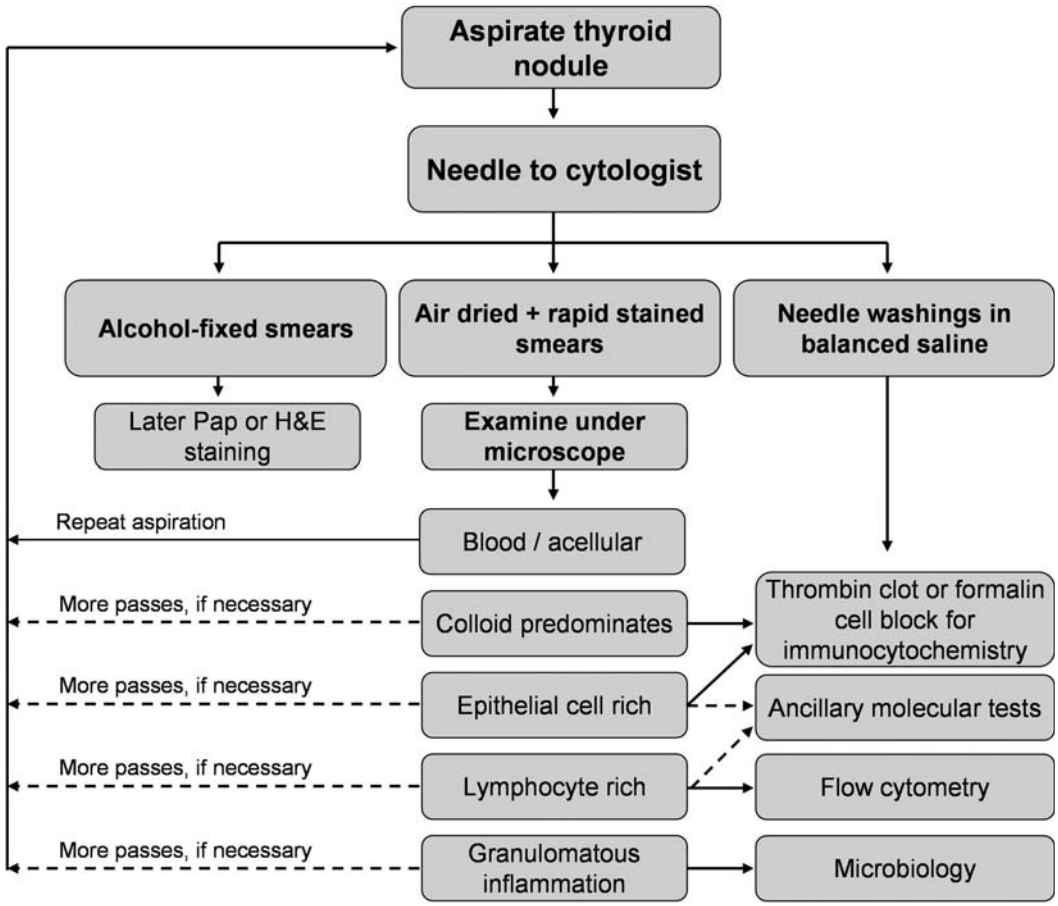

Fig. 3.3. Flow chart showing our local scheme for rapid on-site evaluation of thyroid FNAs.

instance, by analysis of cancer gene profiles for a cohort of 62 thyroid samples, Finley et al. [44] were able to distinguish between benign and malignant thyroid tumors. They reported a sensitivity of 91.7% and a specificity of 96.2% for the detection of thyroid carcinomas of various types, including papillary and follicular carcinomas [44]. However, at the present time, clinical use of specific molecular markers to improve the diagnostic accuracy of indeterminate thyroid nodules is not recommended.

Specimen Adequacy

Acquiring adequate and diagnostic specimens from the thyroid remains one of the most challenging obstacles in thyroid FNA. Currently, criteria for specimen adequacy vary from institution to institution. Several discussions of this issue have been published [8, 9, 11, 24, 25]. Some investigators require that an adequate sample should contain five to six groups of well-preserved and well-visualized follicular cells with each group containing ten or more cells [8, 9, 11]. The Papanicolaou Society of Cytopathology (PSC) has published guidelines [26] that do not specify a certain minimal number of follicular cells, but instead stress the importance of assessing the amount of colloid in determining specimen adequacy (Table 3.1). For instance, a benign colloid nodule may be suggested if a large amount of thick colloid material is present, regardless of the number of follicular epithelial cell clusters. However, one should be cautious in rendering a diagnosis

Table 3.1. Guidelines for the microscopic evaluation of specimen adequacy

Number of follicular cells	Amount of colloid	Interpretation
Numerous	Variable	Adequate for interpretation, diagnosis depends on cellular features
Few	Scanty or Absent	Inadequate or unsatisfactory for interpretation[*,†]
Few follicular cells	Abundant	Benign colloid nodule[‡]
Numerous macrophages, few follicular cells	Variable	Probably benign cystic colloid goitre[§]

[*]One should be cautious in rendering a diagnosis of colloid nodule in a specimen which shows watery colloid, macrophages, and few follicular cells, because aspirates of papillary carcinoma with extensive cystic degeneration may also give rise to specimens with abundant colloid-like material, macrophages, and few follicular cells.
[†]If malignant cells, irrespective of the number, are positively identified in an aspirate, a malignant diagnosis should be made. However, if small numbers of follicular cells show atypical features short of overt malignancy, a "suspicious" diagnosis or a repeat aspiration may be suggested.
[‡]The report should contain a qualifier stating that the interpretation is limited by the paucity of follicular cells and repeat aspirate is recommended if nodule growth is observed on follow-up.
[§]Occasionally, a cystic papillary carcinoma may present a similar pattern. Check for residual solid areas, and re-aspirate if palpable. The risk of malignancy is higher in large (greater than 4 cm) lesions and those that increase in size despite therapy.

of colloid nodule in a specimen showing watery colloid, macrophages, and few follicular cells, because aspirates of papillary carcinoma with extensive cystic degeneration may also display a similar cytological appearance. If a cell sample contains one or two small clusters of malignant or highly atypical cells, it should be reported as malignant or suspicious for malignancy and not as unsatisfactory or inadequate for cytodiagnosis. The British Society for Clinical Cytology (BSCC) is in the process of preparing Codes of Practice for FNA, endorsed by the Royal College of Pathologists, which will be available in 2009.

A repeat FNA may provide diagnostic smears in up to 50% of cases [8]. In the Mayo Clinic experience, repeating the FNA in the cases with initial non-diagnostic needle aspirates revealed diagnostic material in 30–80% of cases [8, 11]. If the re-aspiration is still non-diagnostic, US-guided FNA should be performed [28, 29].

Cytodiagnosis and Diagnostic Categories

Thyroid FNA results are commonly divided into four or five categories [15, 24–27]. In the four-tiered classification system, the FNA results are categorized into nondiagnostic/inadequate, benign, suspicious for neoplasm, and malignant. Typically, a benign cytological diagnosis is reported for 50–90% of the specimens [8, 11, 19, 45, 46]. About 10–30% of FNA specimens may be suspicious for malignancy or indeterminate [8, 11, 46]. A malignant or positive cytological diagnosis varies from 1 to 10% [46]. This categorization does not identify follicular neoplasms, which are known mostly to be benign but require excision to exclude malignancy. For that reason, a five-tiered classification is favored in the UK [15, 47].

In the five-tiered British Thyroid Association (BTA) classification system [15, 47], the FNA results are categorized into Thy1 (nondiagnostic/inadequate), Thy2 (benign/nonneoplastic), Thy3 (follicular lesions), Thy4 (suspicious of malignancy), and Thy5 (diagnostic of malignancy). The details of Thy classification and recommended action are listed in Table 3.2.

Recently, a six-tiered classification system has been proposed at the NCI State of the Science Conference in 2007 in Bethesda on thyroid FNA which can be downloaded from www.thyroidfna/gov/pages/conclusion. Briefly, the NCI Thyroid FNA classification system subdivides thyroid lesions into 1) benign, 2) follicular lesion of undetermined significance, 3) neoplasm (including follicular neoplasm and Hurthle cell neoplasm), 4) suspicious for malignancy, 5) malignant and 6) nondiagnostic

Nondiagnostic or Inadequate FNA Specimen (Thy1)

Inadequate specimens should be labeled "nondiagnostic" or "unsatisfactory." The specimen adequacy criteria (Table 3.1), as described

Table 3.2. Diagnostic categories for fine-needle aspiration (FNA) biopsy of thyroid nodules (BTA classification)

Diagnostic categories		Proposed actions
Thy1	Unsatisfactory, nondiagnostic or inadequate (specify reason)	• FNA should be repeated • Ultrasound guidance may permit more targeted sampling
Thy2	Nonneoplastic (features consistent with a colloid nodule, nodular goiter, cystic goiter, or thyroiditis)	• Two diagnostic benign results 3–6 months apart are required to exclude neoplasia • In patients in a high clinical risk group (e.g., male gender, extremes of age, with other features suggestive of tumor, with a family history, or with a history of irradiation) the decision to proceed to lobectomy may be made even with a benign FNA diagnosis • This decision might also be made if there are pressure symptoms or rapid growth • In addition, the patient should have the choice to have the lesion removed if he/she so wishes
Thy3	Cellular follicular lesions including hyperplastic nodule, follicular neoplasm (adenoma and carcinoma), and Hurthle cell lesions	• Lobectomy or watchful waiting depending on clinical features • Completion thyroidectomy will be necessary if the histology proves malignant
Thy4	Abnormal, suspicious of malignancy (suspicious, but not diagnostic, of papillary, medullary, or anaplastic carcinoma or of lymphoma)	• Surgical intervention indicated for differentiated tumor • Further treatment will depend on the histopathology report • Indication for further investigation for anaplastic thyroid carcinoma, lymphoma, or metastatic tumor
Thy5	Diagnostic of malignancy with unequivocal features of papillary, medullary or anaplastic carcinoma, or of lymphoma or metastatic tumor	• Surgical intervention indicated for differentiated thyroid cancer, depending on tumor size, clinical stage, and other risk factors such as gender and extremes of age • Indication for appropriate further investigation, radiotherapy, or chemotherapy for anaplastic thyroid carcinoma, lymphoma, metastatic tumor

above, should be followed regardless of radiological and clinical findings. The range of inadequate or unsatisfactory specimens reported in the literature ranges from 2 to 21% (mean 17%) [13]. Factors that affect adequacy rate include variable training and technique of operators, the vascular nature of the thyroid, and the variably cellular nature of thyroid nodules [8, 11, 24–27, 45, 46].

- In general, an acceptable rate for inadequate specimens is less than 15%.
- Aspirators who consistently produce high numbers of inadequate samples should be identified and offered training.

Benign or Nonneoplastic Lesions (Thy2)

This group includes lesions with the diagnosis of colloid nodule, multinodular goiter, cystic goiter, or thyroiditis. Whenever possible, a specific cytological diagnosis should be provided.

Benign Colloid Nodule or Multinodular Goiter

Aspirates obtained from multinodular goiters show loosely cohesive sheets of follicular epithelium, colloid, blood, and macrophages. Colloid nodules contain an abundance of colloid with sparse follicular cells. There is considerable variation in the number of cells as well as the type and amount of colloid present. Typical cytological features include [8, 11, 24–27, 45, 46]

- abundant colloid, thick and/or thin (Fig. 3.4);
- small to moderate number of follicular epithelial cells in monolayered sheets, poorly cohesive groups, and single cells. May have oxyphilic or Hurthle cell change;
- variable number of histiocytes and hemosiderin-laden macrophages;
- may have degenerative changes: old blood, debris, fragments of hyalinized stroma.

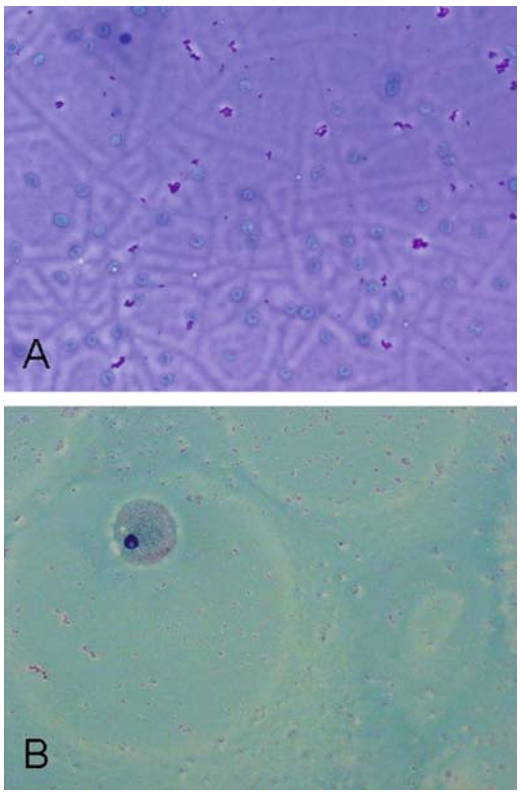

Fig. 3.4. FNA of a benign colloid nodule. (A) Abundant dark blue-stained colloid material with cracking pattern in air-dried smear (Hemocolor staining, ×400). (B) Thin watery colloid with macrophages in fixed smear (Papanicolaou stain, ×400).

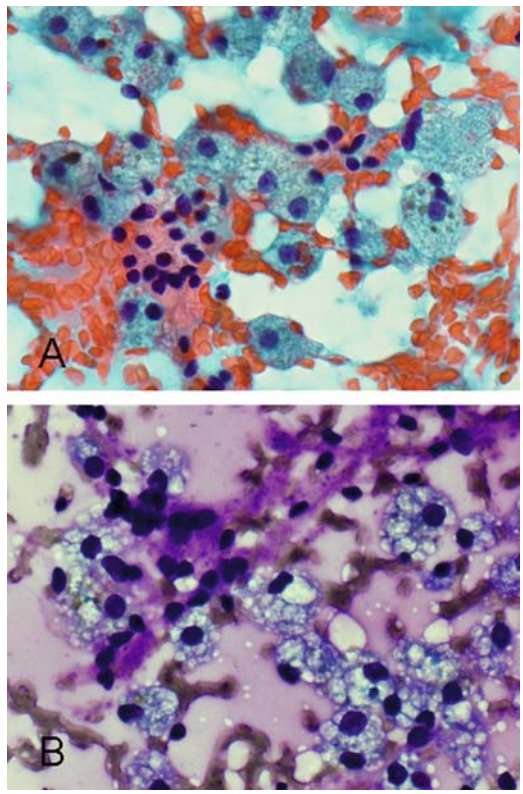

Fig. 3.5. FNA of a cystic goiter shows colloid material admixed with benign follicular epithelial cells and numerous hemosiderin-laden macrophages (A) Papanicolaou stain, ×400. (B) Hemocolor stain, ×400).

Cysts and Cystic Goiter

Benign cysts account for the majority of thyroid cystic lesions. They are formed as the result of hemorrhagic degeneration of a benign colloid nodule. FNA from a benign colloid cyst may show colloid admixed with benign follicular epithelial cells and hemosiderin-laden macrophages (Fig. 3.5). However, any thyroid neoplasm may undergo hemorrhagic cystic change [9, 26, 48]. Of the thyroid neoplasms, papillary carcinoma tends to undergo marked hemorrhagic degenerative change. FNA from the tumor commonly shows a large amount of blood and the cystic lesion tends to recur rapidly [26]. Thus, it is important to keep in mind that

- the presence of cystic change in thyroid tissue does not in itself imply a benign lesion;
- a definitive diagnosis of benign nodular goiter with cystic change requires adequate sampling of any solid component;
- if only cyst fluid-containing macrophages with no epithelial cells is obtained, this should be interpreted as nondiagnostic, as an underlying neoplasm with cystic change cannot be excluded;
- Notably, the gross appearance of cyst fluid is not helpful in distinguishing benign thyroid cyst from neoplastic cyst. One study showed little difference in the prevalence of neoplasm in association with bloodstained fluid, brown turbid fluid or straw-colored fluid [49].

Thyroiditis

Hashimoto's thyroiditis and subacute thyroiditis commonly have fairly distinctive clinical

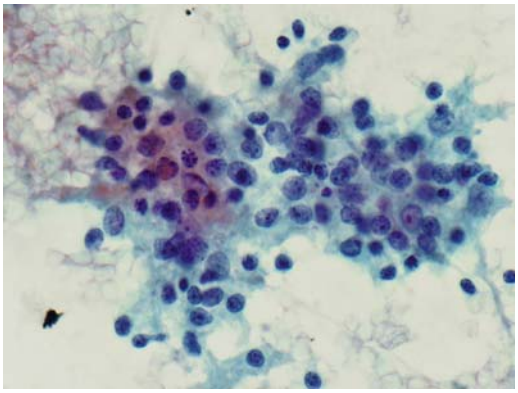

Fig. 3.6. FNA of lymphocytic thyroiditis. A sheet of follicular epithelial cells is infiltrated by small mature lymphocytes and plasma cells (Papanicolaou stain, ×400).

and cytological findings. These lesions may present as a nodular lesion mimicking a thyroid neoplasm.

Hashimoto's thyroiditis is characterized by the presence of numerous lymphoid cells admixed with benign follicular cells (Fig. 3.6) and Hurthle cells. Typical cytological features of Hashimoto's thyroiditis include [9, 24, 25]

- mixed population of lymphocytes and plasma cells;
- lymphohistiocytic aggregates;
- cohesive groups of follicular cells with oncocytic features;
- little or no colloid.

Subacute (granulomatous) thyroiditis is a rare condition in the context of a benign aspirate. Typically, the smear shows multinucleated giant cells, epithelioid histiocytes, and scattered inflammatory cells.

Other Benign Lesions

Graves' disease may rarely present as a nodular thyroid lesion [9, 19, 24, 25]. It yields nonspecific cytological findings. Common cytological findings include

- bloodstained smear with little colloid;
- moderate amounts of follicular epithelium and some follicular or ring structures;
- cells with abundant pale vacuolated cytoplasm; mild nuclear enlargement and moderate anisokaryosis;
- marginal vacuoles of the colloid.

Follicular Lesions (Thy3)

Cellular Microfollicular Lesions

Follicular lesions of the thyroid represent the most problematic area of thyroid FNA [24–26, 50–53]. The major entities included in the differential diagnosis are hyperplastic/adenomatoid nodule, follicular neoplasm (adenoma and carcinoma), and some cases of the follicular variant of papillary carcinoma. Follicular lesions are found in 15–30% of FNA specimens [50–53].

As with frozen section, FNA cannot reliably distinguish between benign and malignant follicular lesions [27]. Specimens from cellular adenomatoid nodule, follicular adenoma, and well-differentiated follicular carcinoma usually give rise to a similar cytological appearance. Definitive diagnosis requires histological examination of the excised nodule to demonstrate the presence of capsular or vascular invasion. The prevalence of malignancy in this group of patients is approximately 15–20% [51–53]. Thus, a diagnosis of follicular neoplasm belongs to the indeterminate category (Thy3) of thyroid FNA classification [15].

Cytological features of follicular lesions include

- cellular, monotonous cell population (more than 70% of specimen) scattered throughout the smear (Fig. 3.7);
- microfollicles and rosettes;
- nuclear overlapping and crowding in syncytial groups of cells without the nuclear features of papillary carcinoma;
- scanty or no colloid (except as inspissated colloid in microfollicles).

Generally, two cytological subcategories of Thy3 can be recognized [25, 26]: cellular follicular lesion (favor hyperplastic or adenomatous nodule) and cellular follicular lesion (favor follicular neoplasm). As described above, this subdivision within Thy3 results in a similar six-tiered classification system proposed at the NCI State of the Science Conference on thyroid FNA (www.thyroidfna/gov/pages/conclusion). Unless there are specific features suggesting malignancy (see below) or nuclear features suggesting papillary carcinoma, it is better not to comment on whether a follicular lesion favors a benign or malignant neoplasm.

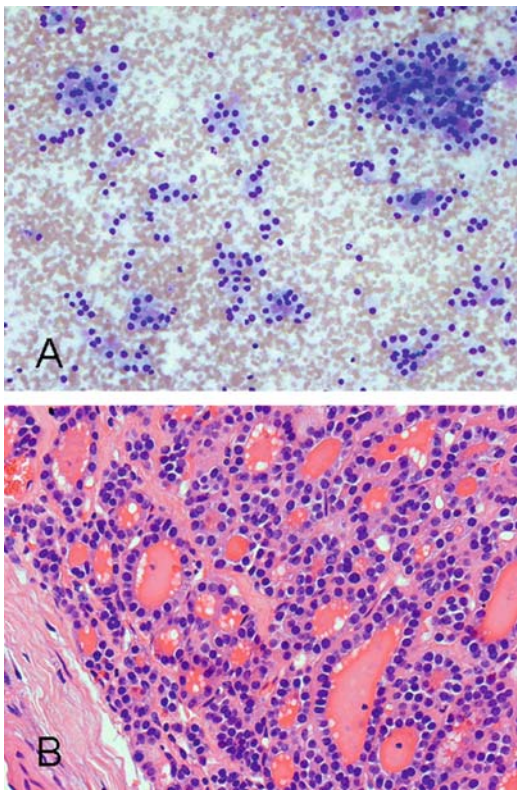

Fig. 3.7. FNA of a microfollicular lesion. (**A**) A cellular aspirate consists of a monotonous population of follicular cells arranged in microfollicular pattern. Cells have round nuclei with no significant nuclear atypia (Hemocolor stain, ×200). (**B**) Excision of the lesion reveals a well-circumscribed follicular adenoma (H&E stain, ×200).

Factors suggesting malignancy include male gender, nodule size over 3 cm and age over 40 years [51]. Some cytological features are also shown to be associated with increased cancer risk. These include an increased nuclear size with marked nuclear atypia including significant nuclear pleomorphism and irregularity [53]. Re-aspiration of a follicular lesion is usually discouraged as it rarely provides useful information.

Hurthle Cell Lesion

This group includes both Hurthle cell adenoma and Hurthle cell carcinoma, which are generally indistinguishable from one another on the basis of cytological examination [8, 54, 55]. It is a diagnostic challenge to separate them from hyperplastic Hurthle cell nodules in Hashimoto's thyroiditis [12, 24, 25, 54, 55]. Thyroid nodules that show exclusively Hurthle cells without a background of thyroiditis on FNAs have a high rate of Hurthle cell neoplasm [24, 25, 54, 55]. On the other hand, a mixture of Hurthle cells and "normal" follicular epithelial cells is more consistent with a hyperplastic nodule and should not be interpreted as evidence of Hurthle cell neoplasm [24, 25, 54, 55].

Hurthle cell lesions are cytologically characterized by

- cellular aspirates containing sheets and clusters of polygonal Hurthle cells with abundant, granular, eosinophilic, or basophilic cytoplasm (Fig. 3.8);

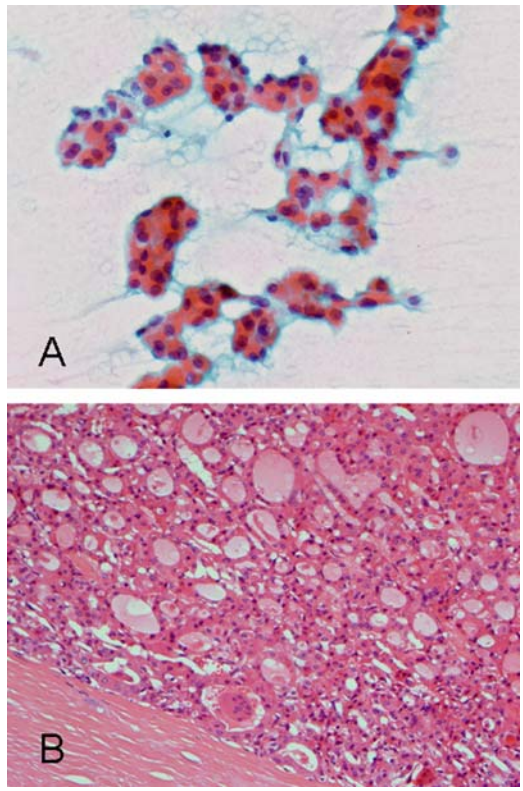

Fig. 3.8. FNA of a Hurthle cell lesion. (**A**) A monotonous population of Hurthle cells arranged in the microfollicular pattern. Cells have abundant, granular cytoplasm and round, central, or eccentrically located nuclei (Papanicolaou stain, ×400). (**B**) The excision biopsy shows a Hurthle cell adenoma (H&E stain, ×200).

- oval nuclei with regular nuclear contours and conspicuous or inconspicuous nucleoli;
- minimal colloid.

Thyroid Hurthle cell lesions fall into the cytodiagnostic category of indeterminate lesions (Thy3), and 13% of Hurthle cell lesions were malignant in one large series [8, 54, 55]. When a Hurthle cell lesion is detected by FNA, surgical excision is usually indicated for further histological study [54].

Suspicious of Malignancy (Thy4)

Many cytopathologists use this category when the cytological features are suggestive of a specific malignancy, but a definitive diagnosis cannot be rendered due to quantitative reasons (i.e., malignant appearing cells, but limited cellularity) or qualitative reasons (i.e., focal or less than well-developed features of malignancy, or an atypical lymphoid population) [15, 26, 27]. The most commonly encountered example of this diagnostic category is "suspicious for papillary carcinoma."

Malignant Lesions (Thy5)

The aspirates in this group are diagnostic of malignancy with unequivocal features of papillary, medullary or anaplastic carcinoma, or of lymphoma or metastatic tumor [12, 15, 24–27]. These lesions commonly show distinctive cytological features that permit correct identification in the majority of cases. In many of these cases, diagnosis should be supported by immunocytochemistry (solid tumors) or flow cytometry (lymphomas).

Papillary Carcinoma

This is the commonest form of thyroid cancer, accounting for up to 80% of thyroid malignancies [56, 57]. It usually presents between 30 and 40 years of age and is three times more common in women [56, 57]. Clinically, it is often indolent, although certain variants are aggressive. It tends to spread locally in the neck, compressing the trachea and may involve the recurrent laryngeal nerve. It can metastasize to lung and bone.

FNA is highly accurate for the diagnosis of papillary carcinomas, particularly for classic or usual type of papillary carcinoma (Fig. 3.9); more than 90% are reported as malignant (Thy5) or suspicious (Thy4) on FNA [8, 9, 11, 24–27].

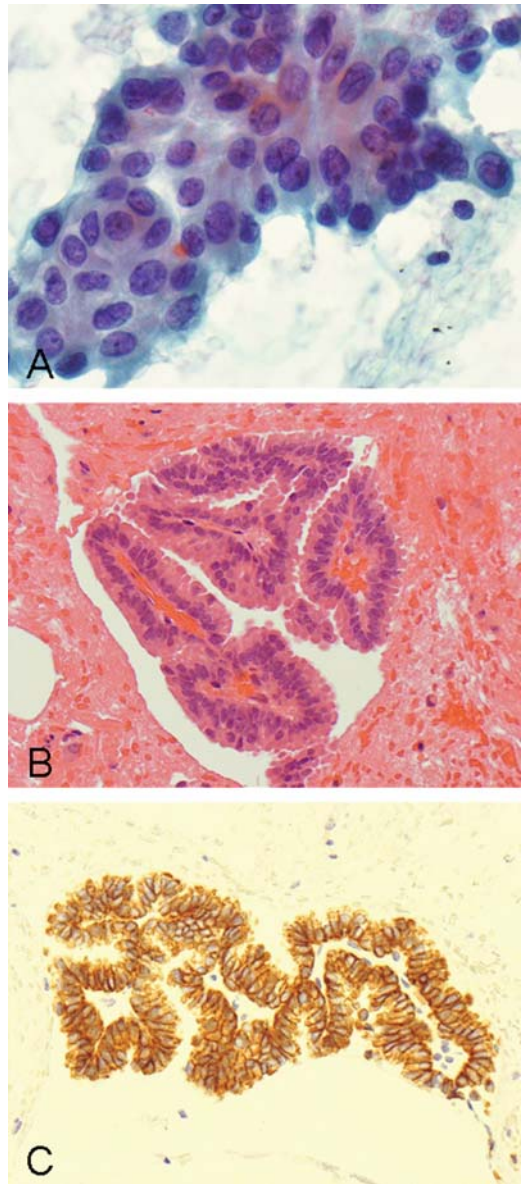

Fig. 3.9. Papillary carcinoma. (**A**) A cluster of tumor cells showing nuclear crowding with nuclear grooves and intranuclear inclusions (Papanicolaou stain, ×400). (**B**) Papillary tissue fragments are seen in a cell block preparation from the needle washings (H&E stain, ×200). (**C**) The lining epithelial cells of the papillary fragments are strongly positive for CK19 (immunocytochemistry, ×200).

Cytological features of papillary carcinoma include

- cellular aspirates;
- syncytial aggregates or sheets of cells. May have papillary cytoarchitecture or psammoma bodies;
- enlarged, oval nuclei with eccentric nucleoli;
- fine, pale chromatin;
- longitudinal nuclear grooves;
- intranuclear inclusions;
- dense squamoid cytoplasm;
- macrophages and debris (evidence of cystic degeneration), multinucleated giant cells and variable numbers of lymphocytes;
- positive immunostaining for CK19, HBME-1, and CD44.

Variants of papillary carcinoma include follicular, diffuse sclerosing, Warthin-like, solid, trabecular, cribriform-morular, oncocytic, tall cell, and columnar cell type [56, 57]. Cytological diagnosis of these less common variants is often difficult.

Poorly Differentiated Follicular Carcinoma

Follicular carcinoma is the second commonest form of thyroid cancer, accounting for about 10% of thyroid malignancies [56, 57]. It is three times as common in women and tends to present between 30 and 60 years of age. On FNA biopsy, malignancy is usually suspected due to the high cellularity, nuclear hyperchromasia and chromatin coarseness (Fig. 3.10). Some tumors may show necrosis and mitotic activity. A cytological diagnosis of insular carcinoma may be suggested if multiple samples of a thyroid mass are markedly cellular, with a cytological pattern sometimes reminiscent of a follicular variant of papillary carcinoma. However, the follicular cells are arranged predominantly in rosettes, their nuclei appear more monotonous, although occasional large cells with pleomorphic nuclei may be seen.

Cytological features of poorly differentiated follicular carcinoma include [9, 24, 25]

- highly cellular smears;
- cells dispersed and in syncytial multilayered clusters;
- nuclear hyperchromasia, coarse chromatin, prominent nucleoli, high nuclear cytoplasmic (N:C) ratio;

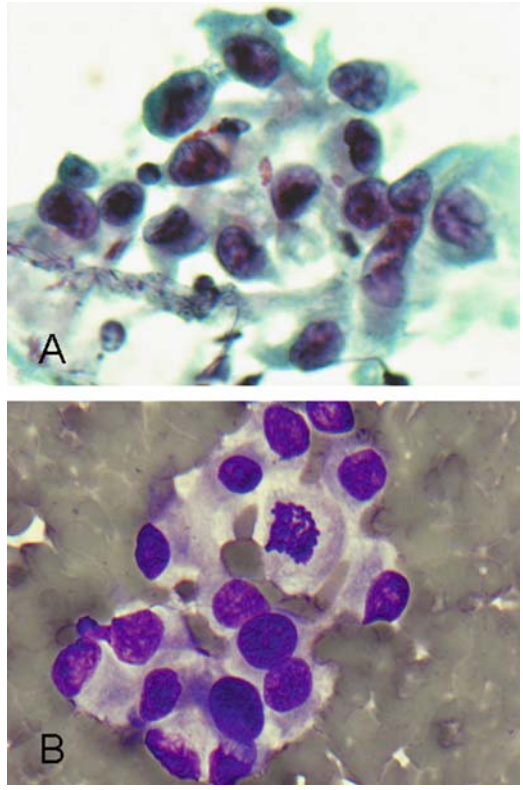

Fig. 3.10. FNA of a poorly differentiated follicular carcinoma. (**A**) Loosely cohesive, pleomorphic tumor cells showing hyperchromatic nuclei and prominent nucleoli (Papanicolaou stain, ×400). (**B**) Similar cells with an apparent mitotic figure are seen in the air-dried smear (Hemocolor stain, ×400).

- may have necrosis and mitotic activity;
- absence of colloid.

Medullary Carcinoma

This accounts for approximately 5% of thyroid cancers [56, 57]. About 25% of patients give a family history. Female preponderance is less marked compared with other thyroid malignancies.

Typically, aspirates from a medullary thyroid carcinoma are hypercellular and show the following cytological features [9, 24, 25]:

- Cellular smears, mainly dispersed cells, some clustering (Fig. 3.11).
- Variable cell pattern, plasmacytoid, small cell, spindle cell.
- Moderate anisokaryosis, may have scattered very large nuclei, bi- and multinucleated forms.

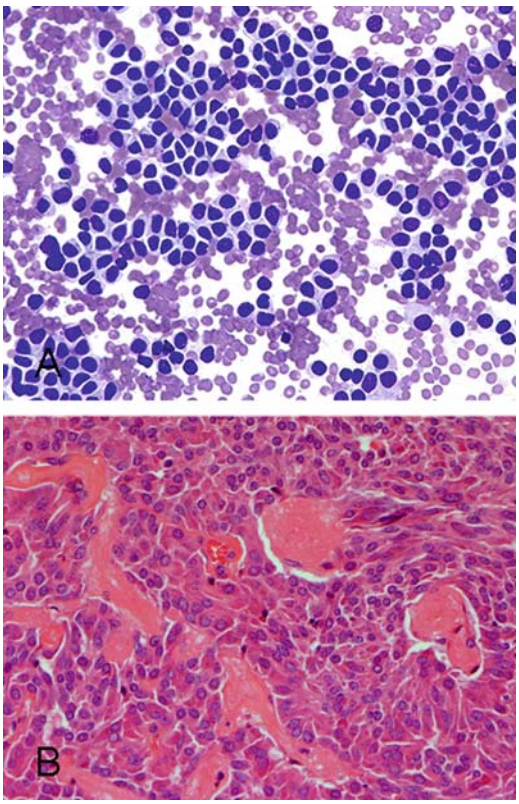

Fig. 3.11. Medullary carcinoma. (**A**) FNA showing dyshesive plasmacytoid tumor cells with eccentrically located round nuclei (Hemocolor stain, ×200). (**B**) Thyroidectomy specimen reveals a solid tumor composed of nests of polygonal tumor cells with abundant eosinophilic granular cytoplasm. Amorphous amyloid stroma is also evident (H&E stain, ×200).

- Indistinct nucleoli.
- Granular "salt-and-pepper" chromatin.
- Background amyloid (approximately 80% of cases), minimal or no colloid.
- Positive immunostaining for calcitonin, (CEA), and neuroendocrine markers.

Anaplastic Carcinoma

This represents less than 2% of thyroid cancers [56, 57]. Women are affected more often than men. It tends to present in the 50 s and 60 s. Half have metastases at presentation and prognosis is poor. Where the diagnosis has not been possible on FNA, core biopsy or open biopsy may assist the diagnosis [9, 24, 25]. Clinical assessment is important to exclude metastatic carcinoma from elsewhere.

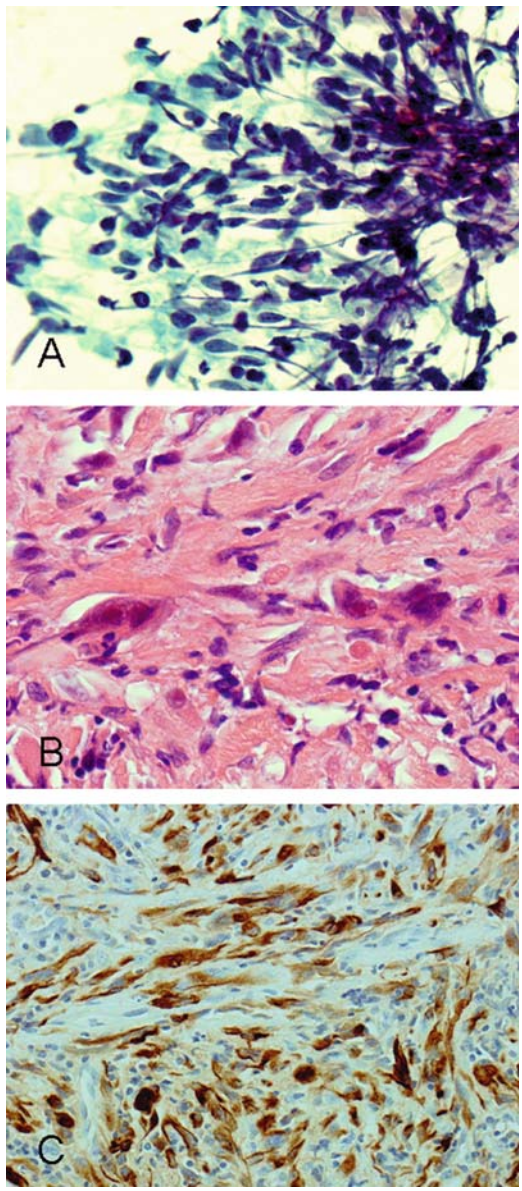

Fig. 3.12. FNA of an anaplastic carcinoma. (**A**) Loosely cohesive spindle-shaped malignant cells with hyperchromatic nuclei and ill-defined cytoplasm (Papanicolaou stain, ×400). (**B**) Biopsy shows sarcomatoid anaplastic tumor cells (H&E stain, ×400). (**C**) Tumor cells are positive for cytokeratin MNF116 (Immunohistochemistry, ×400).

Diagnostic cytological features of anaplastic thyroid carcinoma include

- highly malignant and bizarre cells: spindle cells (Fig. 3.12), giant cells, squamoid cells;

- high-grade nuclear features: marked pleomorphism, dark clumped chromatin, macronucleoli and atypical mitoses.
- necrotic cell fragments, debris, inflammatory background in some tumors;
- positive staining for pancytokeratin excludes sarcoma, lymphoma, or melanoma. However, TTF-1 and thyroglublin stains are often negative.

Lymphoma

Between 2 and 5% of thyroid malignancies are lymphomas [56, 57]. The majority of the thyroid lymphomas are of MALT type and are associated with Hashimoto's thyroiditis [56, 58]. This often causes special diagnostic problems, as a mixed cell population including many plasma cells, suggestive of a florid reactive process, may be seen in smears of low-grade lymphoma. Diagnostic difficulties by FNA biopsy may be further enhanced by the occurrence of residual reactive follicles in low-grade MALT lymphoma. FNA with flow cytometry may provide a diagnosis but core biopsy or open biopsy may be needed to allow immunohistochemical subtyping of the lymphoma, which will have implications for further treatment [12–16].

High-grade diffuse large B-cell lymphoma (DLBCL) generally presents with a rapidly enlarging gland clinically suggesting malignancy. The diagnosis is usually obvious in FNA smears, which show a monotonous population of large lymphoid cells. Hodgkin lymphoma rarely occurs in the thyroid.

Practical points about thyroid lymphomas:

- Approximately 50% present with a single dominant thyroid nodule.
- Phenotypically, 28% MALT, 33% DLBCL + MALT, 38% DLBCL only, 1% follicle center lymphoma. Hodgkin lymphoma, plasmacytoma, and T-cell lymphomas are extremely rare [58].
- It is possible to diagnose this on the basis of FNA where flow cytometry or molecular analysis can be applied to identify a clonal population.
- Core biopsy or open biopsy may assist the diagnosis by allowing immunohistochemistry to be performed in the context of architectural features but molecular analysis may still be required.
- The management of patients with thyroid lymphoma is best given by an appropriate multidisciplinary group specializing in lymphoma management.
- Thyroidectomy is not indicated.

Secondary Tumors

The thyroid is a relatively common site for metastasis in disseminated malignancy [56, 57]. A metastatic tumor can simulate a primary neoplasm. Lung, gastrointestinal tract, breast, kidney, and skin melanoma are the most frequent sites of origin. Cytodiagnosis of metastatic cancer to the thyroid is relatively straightforward as metastatic cancer usually displays a cytological pattern and immunoprofile distinctive from those of a primary thyroid carcinoma [59, 60].

Diagnostic Accuracy and Errors

Thyroid FNA, as with all medical tests, has its limitations; however, when properly applied, it is useful in distinguishing low-risk from high-risk or frankly malignant lesions. In a review of seven large series totaling 18,183 thyroid FNAs, Gharib and Goellner found that the technique had a sensitivity rate varying from 65 to 98% (mean 83%), and that its specificity rate varied from 72 to 100% (mean 92%) [13]. The false-negative rate varied from 1 to 11.5% (mean 5.2%), and the false-positive rate varied from 0 to 7.7% (mean 2.9%) [11]. The overall cytodiagnostic accuracy rate of thyroid FNA approached 95% according to some reported series [8, 9, 11, 24, 25].

Successful FNA has been shown to be highly dependent on operator training and experience [61]. Equally important is slide preparation, which requires experience and skill to provide cellular material that can accurately be interpreted. Inadequate or improper sampling accounts for a significant portion of false-negative errors [62, 63]. For example, nodules smaller than 1 cm in size may be too small for accurate needle placement, and nodules larger than 4 cm in diameter are too large to allow proper sampling from all areas, thereby increasing the likelihood of misdiagnosis. Interpretive errors also account for some false diagnoses [63]. As mentioned above, FNA biopsy of thyroid lymphomas may produce

lymphocytes that can be interpreted as Hashimoto's thyroiditis, accounting for a false-negative diagnosis [64].

Large-Needle Aspiration Biopsy and Core Needle Biopsy

The large-needle-cutting biopsy (also called core needle biopsy) [65, 66] and the large-needle aspiration biopsy (LNAB) [67] techniques employ the largest needles: 14-G Tru-Cut needle for the former and 16–20 G needles for the latter. The operator maintains sterility as a skin nick is performed to permit the insertion of the relatively large needle. Biopsies are performed with the patient receiving local anaesthesia and can be performed with or without ultrasound guidance.

These techniques provide a larger tissue sample that retains its cellular architecture and permits the use of a range of immunohistochemical stains and, therefore, may enable a more precise histological diagnosis [65–67]. Reluctance of clinicians to use core needle biopsy of the thyroid gland, in part, relates to the perceived risks associated with core-needle biopsy of the thyroid gland, in particular the risk of hemorrhagic complications.

Several studies have compared the accuracy and complications of core needle biopsy with that of FNA [65–67]. Some have shown increased diagnostic accuracy when core needle biopsy and FNA are combined, but the problem of distinguishing benign and malignant follicular neoplasms remains. In general, the safety and ease of use of FNA outweigh the slight increase in accuracy achieved by core needle biopsy [65, 67]. A comparison of the advantages and disadvantages of thyroid FNA and core biopsy is listed in Table 3.3.

Recommendations for Thyroid FNA Reporting

The most important part of the pathology report, of course, is the information about interpretation. The report must be clinically relevant and readily understood by clinicians. The following issues should be addressed in the cytopathology report:

- The beginning of the report should include information about specimen adequacy.
- Additional information in the interpretation component of the report includes the diagnostic category that classifies the specimen as unsatisfactory or nondiagnostic (Thy1), benign/nonneoplastic (Thy2), a cellular lesion suggestive or consistent with a follicular neoplasm (Thy3), suspicious for malignancy (Thy4) or malignant (Thy5).
- A specific cytological diagnosis should be provided, and this would be one that identifies and characterizes the nature of the nodule, such as papillary thyroid carcinoma, medullary

Table 3.3. A comparison of the advantages and disadvantages of thyroid fine-needle aspiration (FNA) and core biopsy

Fine-needle aspiration (FNA)	Core biopsy
Easier to perform	More difficult to perform
No need for local anesthesia	Local anesthesia, skin incision, and sterile technique required
Any size nodule can be sampled	Nodules smaller than 1 cm cannot be sampled
Multiple aspirates from different portion of the nodule can be obtained	Only limited cores from the nodule can be obtained
Safer and simpler procedure, fewer or no complications	More complications (bleeding, injury to laryngeal nerve)
Virtually no seeding of tumor	Seeding of tumor reported
Minimal invasive, greater patient acceptance	Less patient acceptance (more pain)
Prompt interpretation is possible	Longer processing time before interpretation
Lower cost, no expensive laboratory equipment needed for preparation and staining of smears	Higher cost, histology laboratory equipment, and personnel required for processing of samples prior to interpretation
Limited material obtained	Multiple sections and special stains can be performed easily

thyroid carcinoma, Hashimoto's thyroiditis, follicular neoplasm, colloid nodule.

- Ancillary test results, such as immunocytochemistry, should be provided on the report and reference made to material for ancillary tests carried out in a separate department (flow cytometry, molecular biology, microbiological culture and sensitivity).
- A final part of the pathology report can include a recommendation or comment section. This is optional, but strongly encouraged when a definitive diagnosis is not rendered. The recommendation may suggest surgical treatment, conservative management with follow-up, repeat FNA or further investigation.

Multidisciplinary Meetings and Quality Assurance

The FNA results should always be taken in clinical context as part of a multidisciplinary team approach to ensure that future action is most appropriate for the patient by integrating information from clinical examination, FNA and biopsy results, nuclear medicine findings, imaging, serology and any other relevant investigations. Good communication with clinicians through multidisciplinary meeting (MDM) is recommended to improve the management of thyroid patients. Where thyroid cancer is managed at a referral center, pathological material should be received in time to allow sufficient time for review at the MDM. The cancer center should provide an expert review by pathologists with a specialist interest in thyroid disease.

Clinical audit is important for achieving best results in delivering an FNA service. Different aspects of the service may be audited to improve the quality of service. For cytology, these include auditing nondiagnostic FNA rates and correlating the histological or clinical outcome of all diagnostic categories, in particular the Thy3 category, which as discussed above, is a heterogeneous group with variable outcomes. One of the main advantages of a formal classification system (such as Thy1–Thy5) is that it facilitates clinical audit and allows correlation of cytology with outcome. However, such systems should not be used alone for diagnosis, which should include a full text report as discussed above.

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4

Thyroid Imaging

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Introduction to Thyroid Imaging

Imaging represents an important diagnostic tool for both endocrinologist and endocrine surgeons. Each imaging modality used to image thyroid lesions has advantages and limitations and when used in combination with sound clinical judgment is useful for certain diseases of the thyroid. Clinicians need to be aware of constantly changing technologies incorporated into the imaging equipment which can affect not only sensitivity and specificity of these tools but can also change long-standing observations in imaging of the thyroid. This chapter discusses imaging of the thyroid gland, with particular emphasis on ultrasound scan (USS), ultrasound-guided fine-needle aspiration biopsy (USS-FNAB), single photon nuclear scanning, positron emission-computed tomography (PET), and computed tomography (CT). Each imaging modality will be discussed in general and then as it pertains to imaging of specific thyroid conditions.

Ultrasound and Thyroid Imaging

Basics of Ultrasound

Ultrasonography, now almost ubiquitously used to evaluate the thyroid and seen universally as the imaging modality of choice was only first used to evaluate palpable abnormalities of the thyroid in the 1970s [1–3]. Luckily this imaging modality is not excessively expensive, is easy to learn and can be used in multiple locations (such as the office, radiology suite, or operating room), due to its portability. USS allows measurement of the thyroid gland, shows tissue echogenicity, vascular flow, and velocity (color-flow Doppler) and is helpful in the accurate placement of needles for diagnostic purposes [4]. It is best if clinicians do not become intimidated by these user-friendly machines and familiarize themselves with all aspects of various machines so they eventually can use a variety of machines available to them.

During ultrasonography high-frequency sound waves are generated and used to view internal organs. Typical diagnostic sonographic scanners operate in the frequency range of 2–18 MHz. The choice of frequency is a trade-off between spatial resolution of the image and imaging depth: lower frequencies produce less resolution but image deeper into the body. When the emitted sound encounters a border between two tissues that conduct sound differently, some of the sound waves bounce back to the transducer, creating an echo. The echoes are analyzed by a computer in the ultrasound machine and transformed into moving pictures of the organ or tissue being examined. Ultrasound is used in a large array of imaging tools and frequently for medical diagnostics.

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Ultrasound waves pass easily through fluids and soft tissues, making the procedure especially useful for examining the thyroid. In contrast, ultrasound waves are unable to penetrate bone or gas, so ultrasound is of limited use for examining regions surrounded by bone, or areas that contain gas or air.

For ultrasound examination of the thyroid, the patient is positioned lying face up with the neck extended and a small pillow behind the upper back. A clear gel is applied to the area of the body being studied to help the transducer make secure contact with the body and eliminate air pockets between the transducer and the skin. The ultrasonographer then presses the transducer firmly against the skin and sweeps it back and forth over the area of interest.

Set up of office-Based Ultrasound

Office-based ultrasound is rapidly becoming an important tool for all endocrine surgeons and endocrinologists and is being currently used by at least 30% or more of all practicing endocrinologists in the office setting. Prior to proceeding with installing ultrasound technology in your office it is wise to follow these simple steps:

1. Assess the need for ultrasound in your particular office:
    - Surgeons are in general highly motivated to provide best treatment for their patients and this technology has been shown to aid in the diagnosis and treatment of patients with thyroid disease.
    - Considerable literature on using ultrasound as an extension of the physical exam.
    - Convenience to you and your patients.
2. Put aside time for training and credentialing such that reimbursement from insurance companies is a viable option:
    - Courses are offered through the American Association of Endocrine Surgeons, American Thyroid Association (ATA), American College of Surgeons, American Association of Clinical Endocrinologists, Head and Neck Society, Endocrine Society, American Institute of Ultrasound in Medicine.
    - Document your competence, clinical correlation for first 50–200 cases.
    - Work closely with radiology colleagues.
3. Look at a broad range of equipment available for purchase and test 2–4 of them in your office with your patient population:
    - Consider image quality, cost, size, ease of use, portability, ability to use different kinds of probes, durability, reliability of service, warranties, resale value.
4. Make a clear plan for documenting your exam and reporting it to the referring physicians:
    - Save digital images and hard copies.
5. Lay out a plan for continued training and updating of equipment on an ongoing basis.

Reporting and Communication of Thyroid Ultrasound

One of the limitations of USS is the high inter-observer variability [5], thus making detailed and consistent communication one of the most important aspects of thyroid ultrasound. Communication channels must be open both ways. While we strongly advocate for surgeon-performed ultrasound in all patients with thyroid diseases, we also urge all endocrine - surgeons to establish a long-term collegial relationship with radiologists who have a focused interest in thyroid imaging and have knowledge about patients with thyroid diseases. We believe that while first pass images can be obtained by an ultrasound technologist, all but the simplest of patients require a thorough second pass evaluation by a dedicated radiologist. This helps increase experience in different diseases of the thyroid, and allows for improved diagnostic yields eventually benefiting the patient. Detailed reviewing of the images and reporting of course can be done after the patient has left the radiology unit based on saved images. If possible images obtained by the radiologist should be accessible to the endocrine surgeon both in the short and in the long term. Standardized reporting by both radiologist and surgeons makes long-term care of patients with thyroid disease easier and more accurate.

Standard Evaluation of the Thyroid by Ultrasound

USS is often the first imaging modality used to investigate a thyroid mass in the euthyroid

Table 4.1. Possible applications of ultrasound in patients with thyroid diseases

- Diagnosis of thyroid aplasia or hypoplasia
- Identification of ectopic thyroid tissue
- In utero investigation of the fetal thyroid gland
- Determination of thyroid size and morphology:
  - Volume
  - Thyroid morphology: diffuse goiter, multinodular goiter, thyroid nodule
  - Echogenicity: hypoechoic, isoechoic, or hyperechoic
  - Blood flow determination
- Evaluation of regional lymph nodes
- Diagnostic fine needle aspiration biopsy
- Treatment: cyst aspiration, ethanol injection, laser photocoagulation

patient (Table 4.1) [6, 7]. USS is advantageous because it is accessible, inexpensive, noninvasive, and avoids ionizing radiation. Ultrasound scanning of the neck is performed by high-frequency transducers (7–13 MHz). Images are obtained in the transverse (axial) and longitudinal (sagittal) planes (Figs. 4.1 and 4.2). Often a sweeping and a painting motion of the wrist is used to obtain images without undue pressure on the neck of the patient. The trachea is often used as the central orienting structure for most ultrasonographers. Lateral and anterior to the trachea lies the thyroid gland on transverse images. Normal thyroid lobes show a homogenous echogenicity, whereas the echogenicity of the sternocleidomastoid and strap muscles (sternohyoid and sternothyroid) are lower [8]. Posterolaterally, the thyroid is bordered by the sonolucent common carotid artery and internal jugular vein and medially by trachea (Fig. 4.1A). The esophagus with its echogenic mucosa can usually be seen behind and to the left of the trachea (Fig. 4.1B). Lymph nodes can be seen medial or lateral to the major neck vessels; lymph nodes in the level VI (pretracheal) compartment are more difficult to see because of shadowing by the tracheal air column.

Ultrasound Evaluation of Thyroid Nodules

Thyroid nodules are very common and may be observed at USS in 50% of the adult population. Many are not palpable, and the incidence of thyroid cancer in incidentally identified or nonpalpable thyroid nodules is the same as that in patients with palpable nodules [9]. Thyroid malignancy is relatively rare and is diagnosed in approximately 25,000 patients per year in the USA [9]. The most common cause of benign thyroid nodules is nodular hyperplasia [9]. Although less than 7% of thyroid nodules are malignant [10], it is critical that they be accurately identified. Ultrasound can accurately determine the size and location of thyroid nodules[10]. All thyroid nodules need to be seen in two planes (longitudinal and transverse) to be considered a true nodule (Fig. 4.2). Size measurements include transverse diameter (width), antero-posterior diameter (AP diameter or

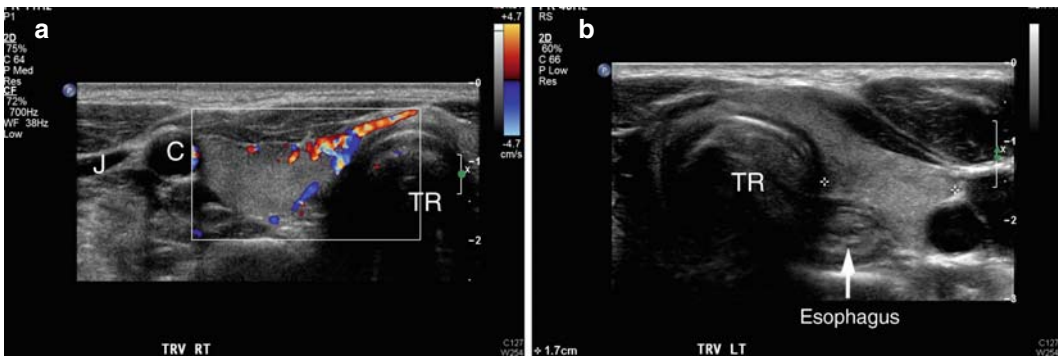

Fig. 4.1. Normal thyroid anatomy seen on transverse ultrasound images **(A)** Normal right with doppler. Trachea is seen as a midline structure (TR), and carotid artery **(C)** and internal jugular vein (IJ) are seen bilaterally (B) Normal left. The esophagus is seen on the left posteriorly.

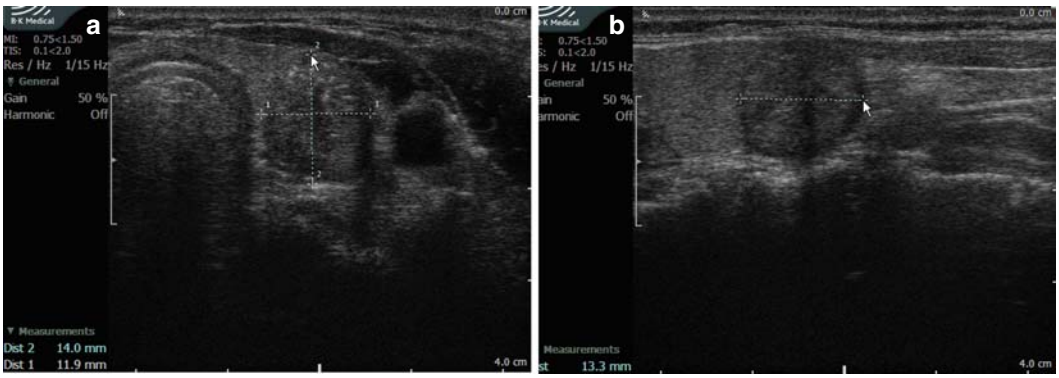

Fig. 4.2. Transverse and longitudinal images of the thyroid with measurement of nodule size in each. (A) Transverse image; (B) longitudinal image.

depth), and longitudinal dimension (length). USS can detect lesions as small as 2–3 mm [2, 11]. Nodules found "incidentally" within a clinically normal thyroid gland are referred to as an "incidental thyroid nodule" or "thyroid incidentaloma" [12]. Their frequency is higher in women, increases with age, and varies between countries [13], but generally there is a high incidence in the population. The diffuse use and high sensitivity of USS is helping the incidental discovery of small and nonpalpable thyroid nodules during carotid, parathyroid, or other ultrasonographic examinations of the neck. Moreover, USS shows one or more additional nodules in about 50% of patients with clinically palpable solitary nodules [12].

The echogenicity of the nodules can vary from hyper- to iso- to hypo-echoic, often even in the same patient. USS examination should search for additional, unsuspected nodules; measure number of nodules and size; record sonographic appearances to assess risk of malignancy and select lesions that require USS-guided FNAB [14, 15]. Several studies have been performed to establish whether specific findings in a thyroid USS alone can differentiate benign from malignant thyroid nodules. While these signs are useful and widely used by those experienced in thyroid USS, ultrasound alone cannot reliably distinguish benign and malignant nodules [16, 17]. Although individual USS features may be of limited value, when multiple signs of thyroid malignancy appear in combination it is at least possible to make some accurate predictions. FNAB and cytological examination have higher sensitivity and specificity, and are considered the best single test in all patients with thyroid nodules; better than thyroid USS alone [18]. Most benign thyroid nodules are hypoechoic. USS patterns predicting thyroid malignancy include hypoechogenicity of the nodule, microcalcifications, central (intranodular) increased vascularity and absence of a halo sign (Table 4.2) (Fig. 4.3).

The risk of malignancy in thyroid nodules occurring within a multinodular goiter (MNG) has not been completely clarified, but some authors find a similar frequency in uni- and

Table 4.2. Ultrasound characteristics of more commonly associated with benign and malignant nodules

Features	Benign	Malignant
Echogenecity	*Hyperechoic*	*Hypoechoic or heterogeneous*
Margins	*Smooth border or complete halo*	*Irregular border or invasion into adjacent tissue*
Colloid	*Comet tail sign*	–
Calcifications	*Peripheral (eggshell)*	*Microcalcifications*
Vascularity	*Peripheral*	*Intranodular/central*
Shape	*Flattened*	*Rounded*
Lymphadenopathy	*Absent*	*Present*
Cyst	*Thin walled*	*Thick walled*

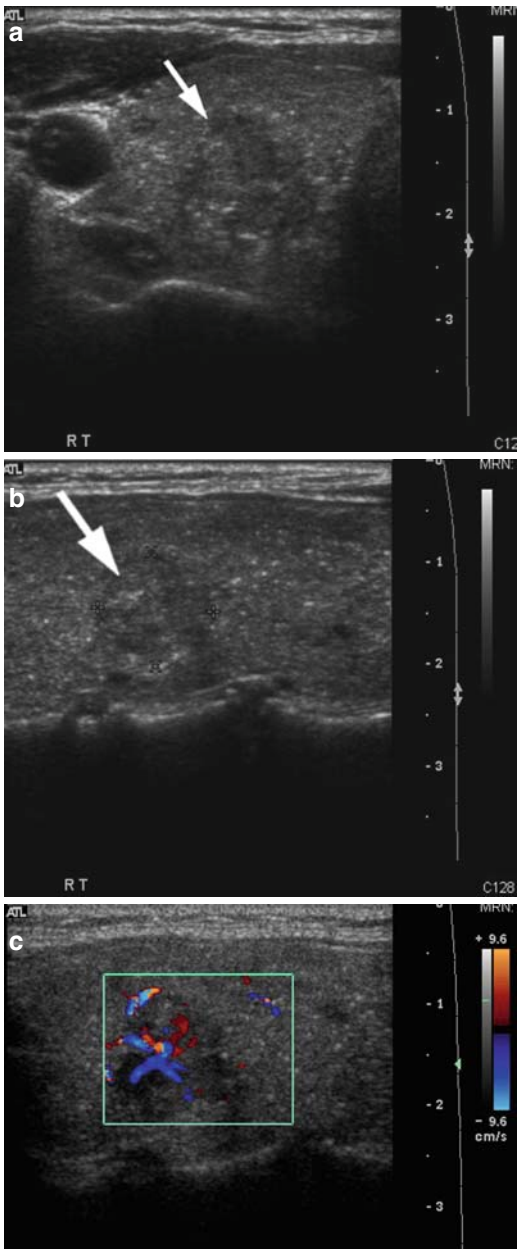

Fig. 4.3. Transverse (**A**) and longitudinal (**B**) thyroid ultrasound images of a suspicious thyroid nodule. This nodule is irregular, hypoechoic, has microcalcifications, and increased intranodular vascularity on Doppler imaging (**C**).

MNGs. The possibility of thyroid malignancy should be considered in all patients with MNGs, and the use of USS guidance has been shown to enhance the diagnostic efficacy of FNAB providing a decrease in nondiagnostic rates from 15% to between 3.5 and 7% [19, 20]. In addition, it has been also recommended that nodules less than 10 mm, detected incidentally, do not require an FNAB. However, thyroid malignancy was found in 6% of nonpalpable lesions of 8–15 mm in size in MNGs and in 9% in solitary thyroid nodules and the risk was similar in nodules smaller or greater than 10 mm [10, 21]. Biopsy recommendations for patients with multiple nodules seen on an USS survey is presented in Table 4.3 [14].

Table 4.3. Biopsy recommendations for patients with multiple thyroid nodules using ultrasound

Guidelines	Recommendation
AACE[62]	In multinodular thyroid glands, the cytologic sampling should be focused on lesions characterized by suspicious US features rather than on larger nodules
ATA[63]	If two or more thyroid nodules >1–1.5 cm are present, those who have a suspicious US appearance should be aspirated preferentially
SRU[80]	In patients who have multiple discrete nodules, the selection should be based primarily on US characteristics rather than nodule size

AACE: American Association of Clinical Endocrinologists; ATA: American Thyroid Association; SRU: Society of Radiologists in Ultrasound; US: ultrasonographic.

Ultrasound Evaluation for Thyroid Goiter

The diagnosis of goiter is based on physical examination, though accurate measurements are difficult without the aid of ultrasound [22]. Using this technique thyroid volume (in normal adults subjects) ranges from 5 to 20 ml and is related to age and body weight in both sexes [23]. Thyroid ultrasound is not able to completely characterize intrathoracic extensions of the thyroid [24, 25,]. Patients with goiter often have them followed by ultrasound, sometimes many times during their lifetime, though generally decision making about surgical intervention is often based on clinical grounds. Thyroid volume is measured by real-time USS and

length × width × thickness of the thyroid lobe multiplied by factor $\pi/6$, correspond to a rotation ellipsoid, while the best calculated volume of the lobe is obtained by multiplying with the optimized correction factor $f = 0.479$; average error of this method is 16%.

Multinodular goiter: Clinical evaluation of patients with MNG is inaccurate and up to 50% of subjects with a solitary palpable nodule or a diffusely enlarged gland actually have multiple nodules when investigated by USS [21]. It has been recommended that all patients who have a nodular thyroid, with a palpable solitary nodule or a MNG should be evaluated by USS [26, 27]. The echogenicity of the nodules can vary from hyper- to iso- to hypo-echoic, often even in the same patient. USS examination should search for additional, unsuspected nodules; measure nodule, number, and size; record sonographic appearances to assess risk of malignancy and select lesions that require USS-guided FNAB [14].

Ultrasound Evaluation of Diffuse Diseases of the Thyroid

Nonautoimmune nontoxic diffuse goiter appears on USS as diffusely enlarged thyroid lobes with a uniform or slightly irregular echogenicity. A diffuse reduction of thyroid echogenicity has been seen in autoimmune thyroid disease (AITD), which includes chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), Graves' disease, and subacute thyroiditis [28, 29].

In *Hashimoto's thyroiditis,* the most common of the chronic thyroiditides and the most common thyroiditis in children, several patterns are described: the thyroid gland can be normal in size or enlarged, showing heterogeneous echogenicity or multiple hypoechoic or hyperechoic areas separated by fibrous strands. In end-stage disease, the thyroid gland can become small and fibrotic, resulting in heterogeneous echo structure [6, 7, 28, 29]. USS cannot distinguish autoimmune thyroiditis from non-Hodgkin's lymphoma.

Thyroid lymphoma occurs almost exclusively in the thyroid gland of patients with Hashimoto's thyroiditis as a rapidly growing mass in the thyroid gland. The most common clinical manifestations are characterized by an enlarging goiter and compressive symptoms [30]. On USS lymphoma has a characteristic asymmetrical pseudocystic pattern [30].

Graves' thyrotoxicosis patients have an abnormal thyroid USS pattern characterized by a diffuse low echogenicity with variable degrees of increased blood flow. Color Doppler USS may be a useful, noninvasive, and rapid method also for differentiating subacute thyroiditis from Graves' disease [31]. During the acute stage of subacute thyroiditis, color Doppler USS shows low echogenicity without increased tissue vascularity in the affected swollen thyroid [31]. In the recovery stage, color Doppler ultrasonography showed isoechogenicity with slightly increased vascularization. Vascularization becomes normal at 1-year follow-up time [31]. Conversely, marked vascularization was observed in patients with untreated Graves' disease [31]. Moreover, on USS subacute thyroiditis is characterized by an enlarged thyroid gland with some hypoechoic areas [32]. Interestingly, methimazole (MMI) treatment induces changes in thyroid hypoechogenicity, mainly in patients who subsequently go into remission. The absence or a low grade of thyroid hypoechogenicity after MMI treatment seems to be a favorable prognostic indicator of remission in Graves' disease. Therefore, the evaluation of thyroid echographic pattern can be considered a useful prognostic tool in patients with Graves' thyrotoxicosis [33, 34]. Color flow Doppler USS can distinguish nodular variants of Graves' disease from nonautoimmune forms of toxic MNG [35]. Nodular variants of Graves' disease are characterized by nodules with normal vascularity surrounded by diffuse parenchymal hypoechogenicity with increased color flow Doppler signal and maximal peak systolic velocity; whereas nonautoimmune toxic MNG shows an increased intra- and perinodular color flow Doppler signal and peak systolic velocity and a normal extranodular vascularity has been described [35]. Interestingly, it has been reported that in patients with thyrotoxicosis factitia, the thyroid gland shows a normal volume and echogenicity at USS and absent hypervascularity or minimal intrathyroidal vascular spots at color flow Doppler USS [36].

Amiodarone-induced thyrotoxicosis (AIT) occurs both in abnormal thyroid glands (nodular goiter, latent Graves' disease) (type I AIT) or in apparently normal thyroid glands (type II AIT). Distinguishing the two forms is very important clinically, because type I AIT responds to MMI and potassium perchlorate

combined treatment, whereas type II AIT is managed by glucocorticoids [37]. Color flow Doppler USS is a technique that shows intrathyroidal blood flow and provides real-time informations on thyroid morphology and hyperfunction, representing a valuable tool for a quick differentiation between the two types of AIT (hypervascularity in patients with AIT type I and absent vascularity in patients with AIT type II). Therefore, the application of Color flow Doppler USS has been shown to be useful in patients with AIT, permitting an appropriate treatment and so a rapid control of thyrotoxicosis.

Ultrasound Evaluation of Thyroid Cysts

Thyroid cysts are benign lesions, which on USS show a low or no echogenicity or with few echoes in the presence of debris or necrotic tissue. By USS, 15–25% of solitary thyroid nodules are cystic [21]. Some studies indicate a lower frequency of malignancy in a cystic than in a solid thyroid lesion [21], and most cysts originate from benign thyroid tissue (Fig. 4.4A) [21]. The treatment of choice is aspiration, but the recurrence rate is 10–80% depending on the number of aspirations and cyst volume [21]. Some benign cystic nodules resolve spontaneously [21]. Indications for therapy are symptoms of compression. Smaller cysts (2–3 ml) are generally best left untreated [21]. If larger, it is possible to perform aspiration and FNAB of any residual nodule.

Ultrasound-Guided Fine-Needle Aspiration Biopsy

Ultrasound can also used to guide FNAB, which aids in positioning of the needle within the lesion. The needle tip can be followed ultrasonographically as it travels and then enters a nodule or suspicious lesion in the thyroid. FNAB is safe, simple, and accurate. It is done in an outpatient setting, and repeated aspirations may be done [38]. FNAB in general is highly accurate and overall reduces the number of patients referred for surgery. FNAB reliability may vary widely from one group to another, with a sensitivity ranging from 57 to 93% [39, 40]. Image-guided FNAB has reported accuracy of more than 95% [7]. USS-guided FNAB allows more material to be obtained for sampling in order to exclude thyroid cancer reducing potential false-negative diagnoses to about 1–5% [38, 41]. Finally, ultrasound-guided FNAB improves the accuracy and reduces the rate of nondiagnostic FNAB of smaller thyroid nodules [42], increasing diagnostic precision and significantly affecting thyroid practice. In addition, USS and USS-guided FNAB can be used to [43] characterize and detect clinically occult thyroid bed tumor recurrence and lymph node metastases.

Ultrasound Evaluation of Thyroid Cancer

Thyroid ultrasound is a mainstay diagnostic tool before and after treatment for all patients

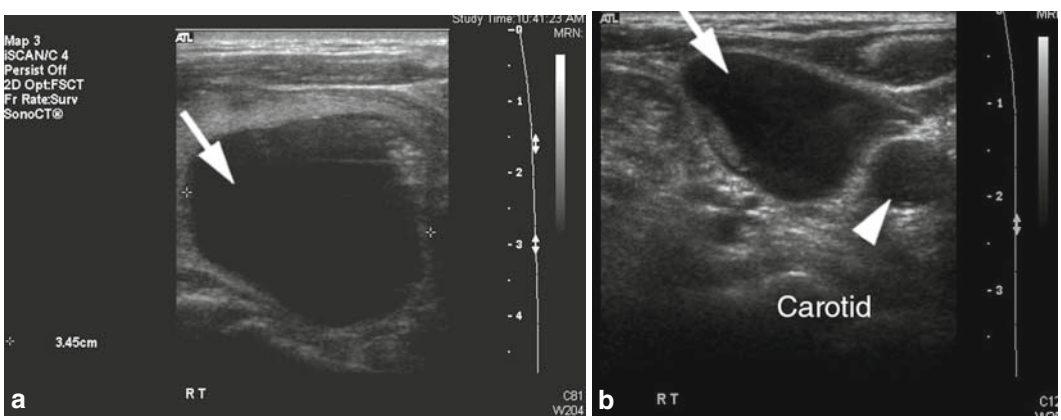

Fig. 4.4. (**A**) Anechoic right thyroid cyst. (**B**) Cystic right-side lymph node, lateral to right carotid, FNA showed papillary carcinoma.

with thyroid cancer. The incidence of differentiated thyroid cancer (DTC) has increased over the past few decades possibly due to more people being diagnosed as a result of extensive screening especially with ultrasound.

Screening for thyroid cancer with USS: Because of the high prevalence of small, clinically inapparent thyroid nodules and the minimal aggressiveness of most thyroid cancers, USS should be used as a screening test only if well-known risk factors are present [14]. Sonographic examination should be ordered for all patients who have a history of familial thyroid cancer, multiple endocrine neoplasia type 2, or childhood head/neck history irradiation, even if the thyroid is normal by palpation [26, 44].

USS features of thyroid cancer: Ultrasound features more commonly associated with thyroid cancer are summarized in Table 4.3. The specificity of USS features for diagnosing thyroid carcinoma varies from 85 to 95% for microcalcifications (small intranodular punctate hyperechoic spots, with scanty or no posterior acoustic shadowing), from 80 to 87% for solid hypoechoic appearance, from 83 to 85% for irregular or indistinct nodule margins, and about 81% for chaotic and increased intranodular vascularity [9, 10, 45, 46]. In addition, some authors report that a nodule shape taller than wide may be suggestive of malignancy [47]. The predictive value of these USS features for cancer is in part diminished by their low sensitivity (29.0–59.2%, 55.1–77.5%, and 74.2%, respectively), and no USS sign by itself can reliably predict malignancy. The association of hypoechoic appearance of the nodule with at least one or more USS features suggestive of malignancy effectively indicates a subset of nonpalpable thyroid nodules at higher risk for malignancy [10, 46]. The presence of at least two suspicious sonographic criteria reliably identifies 85–93% of thyroid gland neoplastic lesions, thus decreasing the number of USS-FNAB procedures to about *one third* of the nonpalpable nodules (Fig. 4.3) [10, 48, 49].

The finding of adenopathy, or presence of a cystic mass on ultrasound in the anterior or lateral neck compartments on USS examination is suspicious for thyroid cancer, even if the thyroid itself is otherwise normal, given the well-described risk of nodal metastasis from an otherwise unrecognized papillary microcarcinoma [14] (Fig. 4.4B).

Ultrasound Evaluation for Thyroid Cancer Recurrence

In the last decade several advances have been developed to aid in the early detection of recurrent thyroid cancer [50]. These include (1) sensitive, reliable, and reproducible thyroglobulin (Tg) assay that biochemically detects the earliest sign of cancer recurrence; (2) development of recombinant human thyroid-stimulating hormone (rhTSH) that allows scanning and Tg stimulation without thyroid hormone withdrawal; (3) high-resolution ultrasound of the postoperative neck to identify early lymph node recurrence. Neck ultrasonography is useful in the follow-up of patients with DTC and in many centers have replaced diagnostic radioactive iodine scanning as the modality of choice for follow-up of patients [27, 51]. Sensitivity of US for the diagnosis of neck recurrence ranges from 70 to 100% [52, 53, 54]. Using these new tools, especially Tg after rhTSH stimulation and neck ultrasound combined with ultrasound-guided FNAB of suspicious lymph nodes, sensitivity of thyroid cancer surveillance has improved. Since most thyroid cancer metastasizes to the neck, and it is rare for thyroid cancer to spread elsewhere without neck lymph node involvement, neck ultrasound has proven very helpful in locating early recurrent disease even before serum Tg is elevated. It is also valuable in following patients with positive anti-Tg antibodies (anti-TgAb) [50]. Identifying and evaluating lymph nodes should be done with high-resolution ultrasound using a 10- to 14-MHz transducer with Doppler capability to assess vascularity [50], concentrating on the thyroid bed and jugular lymph nodes, although metastatic lymph nodes may occur anywhere in the neck [50].

Metastatic lymph nodes tend to be large, round, hypoechoic, hypervascularized with a loss of hilar architecture. The short to long axis ratio (S/L) is a useful way to detect lymph node metastasis as opposed to the long axis alone. In other words, the lymph node exceeding 10 mm in long axis and with S/L over 0.5 showed a much higher incidence of metastasis than S/L under 0.5 [55, 56, 57]. In DTC, metastatic lymph nodes may also demonstrate specific features such as hyperechoic punctuations or microcalcifications and cystic appearance

[58, 59, 60]. Confirmation of malignancy of suspicious lymph nodes found on USS is usually recommended and consists of an FNAB for cytology and Tg determination in the aspirate fluid [61]. Cystic appearance, hyperechoic punctuations, loss of hilum, and peripheral vascularization can be considered major ultrasound criteria of lymph node malignancy. Lymph nodes with cystic appearance or hyperechoic punctuations are highly suspicious for malignancy. Lymph nodes with a hyperechoic hilum should be considered as benign. Round shape, hypoechogenicity, and the loss of hilum taken as single criteria are not specific enough to suspect malignancy [62]. Those performing ultrasound should make a map of the potentially affected lymph nodes to aid the surgeon in identifying and excising the correct lymph node basin. Surgeon performed ultrasound may be of additional help.

Single Photon Nuclear Medicine Imaging

Commonly Used Radionuclides

Thyroid scintigraphy provides a visual display of functional thyroid tissue following the administration of a radionuclide that concentrates in thyroid tissue. It can provide valuable information regarding both thyroid anatomy and function and can play an integral role in the diagnosis and management of thyroid disease. Iodine or its ionized form (Iodide or I^-) is an essential component of the triodothyronine (T3) and thyroxine (T4) and is accumulated in the thyroid, where it plays a critical role in the physiology and pathophysiology of the gland. The transport of iodide by the sodium/iodide symporter (NIS) is the first event in thyroid hormogenesis. The NIS is a protein located on the basolateral membrane of the thyroid follicular cells by which the thyroid concentrates iodide and it has been cloned and characterized [63, 64]. Under physiological conditions the expression of NIS in thyroid cells is mainly dependent on TSH [65]. Iodide transport by NIS also occurs in some extrathyroidal tissues, such as breast, salivary gland, and gastric mucosa, though differently regulated [65]. NIS mediates the first and crucial step in the process of supplying iodide to the thyroid gland for thyroid hormone synthesis. After the step of iodide transport into thyroid follicular cells using the NIS, iodine is then passively translocated via an I^- channel across the apical membrane into the colloid.

There are different iodine radionuclides (summarized in Table 4.4) but only iodine-123

Table 4.4. Common isotopes used in thyroid imaging

Radionuclide	Half-life	Emission	Dose mCi (MBq)	Clinical application
I-127	Nonradioactive	None	–	Fluorescent scanning
I-123	13.2 h	γ 159 keV	0.1–0.4 (3.7–14.8)	Routine thyroid scanning; Whole-body scanning
I-131	8.09 days	γ 364 keV	1–5 (37–185)	Whole-body scanning, therapy for benign and malignant thyroid disorders
I-124	4.2 days	β^+ positron emitter	–	Iodine PET-scanning therapy
I-125	60 days	γ 25-35 keV		In vitro applications
Tc-99m-Tc O_4	6 h	γ 140 keV	1–10 (37–370)	Routine thyroid scanning
Tl-Tl-201	73 h	γ 135-167 keV	2–4 (74–148)	Follow-up recurrent thyroid cancer
Tc-99m-sestamibi	6 h	γ 140 keV	15–20 (555–740)	Diagnosis of thyroid cancer patients with elevated thyroglobulin levels and negative I-131 scan
In-111-pentreotide	2.5 days	γ 172 keV γ 247 keV	3.3 (122)	Noniodine concentrating thyroid cancer scanning; Medullary thyroid cancer scanning

(I-123) and iodine-131 (I-131) are used routinely for thyroid-imaging in nuclear medicine, always administered by mouth [7]. *Iodine-131* (half-life 8.1 days) was the first radionuclide to be used for imaging. The 364-keV gamma emission of I-131 enables scintigraphic imaging, but this energy is higher than is optimal for gamma cameras resulting in poor spatial resolution of I-131 scans performed even with high-energy collimators. Given the high radioactive burden, principally due to its beta emissions, and the poor spatial resolution of the images, I-131 is unsuitable for routine diagnostic thyroid nuclear scan of benign thyroid disorders [66]. I-131 is mainly applied in diagnostic and post-treatment whole-body scanning in patients with thyroid cancer [67]. Conversely, *Iodine-123* is a gamma emitter with favorable characteristics (physical half-life: 13.3 h; gamma energy: 159 keV), but because a cyclotron was required for production, its availability used to be limited, though now it is routinely available for everyday use [66]. Many nuclear medicine departments now routinely use I-123 for routine thyroid scanning and for diagnostic whole-body scanning.

There are also noniodine radionuclides used for thyroid imaging such as *Technetium-99m pertechnetate (Tc-99m)*, which has become a tracer commonly used for thyroid scintigraphy. Tc-99m compared with I-123 has the following advantages: daily availability in every nuclear medicine unit, a shorter physical half-life (6 h), and a preferable favorable energy (140 keV) for scintigraphic imaging. Intravenously administered Tc-99m is loosely bound to plasma proteins and rapidly moves out of the intravascular compartment, is transported by the NIS into the follicular thyroid cell but is not organified. The thyroid uptake of Tc-99m increases within the first 15 min after intravenous administration (influx > efflux), showing a plateau phase between 15 and 30 min and decreases after 30 min. In comparison with I-123, Tc-99m has a lower radiation dose to the thyroid, but a larger effective dose to the whole body. Iodine is very heavily concentrated in the thyroid whereas Tc-99m is not. Thus, the dose to the thyroid is greater with I-123, but the effective dose is higher with Tc-99m. The range of normal uptake of Tc-99m is 0.25–3% of the injected dose and the peak is earlier in a hyperthyroid gland [68].

Less Commonly Used Radionuclides

Other noniodine radionuclides are: *Thallium-201* (Tl-201) was historically used in follow-up study of postoperative patients with thyroid cancer [69]; *Tc-methoxyisobutlylisonitrile-99m (Tc-sestamibi-99m)* shows optimal image resolution and was used in those patients with abnormal thyroglobulin value and negative I-131 nuclear scan [70]; *In-pentreotide-111*, a radiolabeled somatostatin analog (an octreotide analog), is occasionally useful in cases of thyroid cancers that do not have iodine uptake such as medullary carcinoma or other noniodine avid DTCs, such as some Hurthle cell neoplasms. Use of both Tl-201 and Tc-methoxyisobutlylisonitrile-99m (Tc-sestamibi-99m) has been replaced by PET/CT in follow-up of DTC patients with iodine nonavid disease. [71]

Uptake and Thyroid Scintigraphy

Thyroid scintigraphy is used in the differential diagnosis of hyperthyroidism, to distinguish other causes of thyrotoxicosis from hyperthyroidism, to help calculate therapeutic dose of I-131 and to detect intrathyroidal defects in organification. Prior to thyroid scanning patients should avoid all thyroid hormones or antithyroid medications, excess of iodine ingestion, and injection of radiographic contrast media [67]. Radioiodine uptake value may be measured early at 4–6 h and/or late at 24 h; a higher uptake is occasionally seen on the early measurements in patients with severe hyperthyroidism [67]. It is generally possible to predict 24-hour uptake from 4- or 6-hour uptake values with a low potential error [72].

Increased uptake is typical in hyperthyroidism, iodine deficiency, and pregnancy (nuclear scan tests should generally not be performed in pregnant women), although occasionally uptakes are used by some endocrinologists during pregnancy to distinguish Graves' from thyroiditis recovery phase of thyroiditis, lymphocytic thyroiditis, rebound after suppression of thyrotropin, rebound after withdrawal of antithyroid medication, lithium carbonate therapy, amiodarone, nontrapping defects of thyroid hormonogenesis.

Causes of *decreased uptake* include primary hypothyroidism, destructive thyroiditis (subacute thyroiditis, silent thyroiditis, postpartum thyroiditis) thyroidectomy, I-131 treatment,

external neck radiation, central hypothyroidism, thyroid hormone, excess iodine, dietary variations, dietary supplements, radiological contrast, amiodarone, topical iodine, medications other than those containing iodine, antithyroid drugs, perchlorate, thiocyanate, sulphonamides, sulphonylurea, and high-dose glucocorticosteroids [67].

Generally scintigraphy is not used routinely to evaluate thyroid nodules except in those with a suppressed thyroid-stimulating hormone level, in whom it is more likely to find a hyperfunctioning nodule. A particular thyroid nodule by nuclear scan analysis can be described as "cold" (nonfunctioning) or "hot" (hyperfunctioning). A functioning "hot" thyroid nodule is rarely malignant though there are rare cases of patients harbouring malignancy in a "hot" nodule [73, 74, 75, 76, 77, 78]. A nonfunctioning thyroid nodule at scintigraphy is commonly considered to indicate an increased risk of thyroid malignancy; however, overall only 5% of nonfunctioning "cold" nodules are malignant [15]. Therefore, thyroid scintigraphy is only useful when a "hot" nodule is detected.

Thyroid Scintigraphy in Patients with Hyperthyroidism

Thyrotoxicosis is caused by an excess of circulating free T4 and T3. Since the three most common causes of hyperthyroidism are well distinguished by thyroid scanning, this remains one of the most common reasons thyroid scanning is used. The causes of thyrotoxicosis on nuclear scan imaging can be distinguished based on the pattern of iodine uptake. Patients with hyperthyroidism and diffuse high uptake have Graves' disease – rarely TSH-secreting pituitary tumors, placental tumors (choriocarcinoma, hydatiform mole). Patients with hyperthyroidism and focal high uptake are toxic MNG and single autonomous nodule, – rarely thyroid cancer (follicular cancer) and struma ovarii. Hyperthyroid disorders with low uptake are thyroiditides, factitious thyrotoxicosis, thyrotoxicosis medicamentosa, excess iodine exposure [67].

Graves' disease (associated with uniform high intake of iodine) is characterized on nuclear scanning (Fig. 4.5A) by a diffusely enlarged thyroid gland and both early and late uptake are uniformly increased (often 50–80% at 24 h). In patients with *toxic multinodular goiter*, the hyperfunctioning nodule(s) show somewhat lower 24 h radioiodine uptakes which may be in the normal range (often 20–40% at 24 h). Due to the suppressed TSH, normal tissue is not visible. *Destructive (subacute) thyroiditis* shows a reduced uptake $\leq$2% [67, 79]. In patients with a *single toxic adenoma (hyperfunctioning nodule)* (Fig. 4.5B), a single

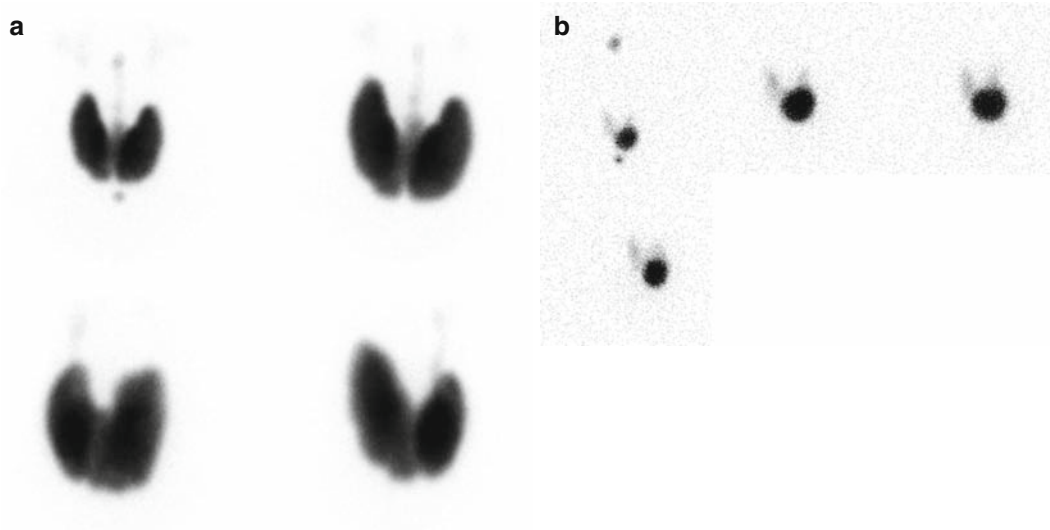

Fig. 4.5. Thyroid scan (I-123) in a patient with Graves' disease (**A**) and a single autonomous nodule (**B**).

focus of increased uptake is seen on thyroid scanning. Solitary toxic thyroid nodules are rarely malignant and generally standard I-123 thyroid scanning is not used in patients with solid nodules unless the serum TSH is suppressed. In those patients with TSH suppression, when a "hot" solitary functioning nodule is seen with suppression of extranodular uptake in thyroid tissue, the "hot" nodule is rarely malignant. There can be exceptions to the rule and both endocrinologist and surgeons may still wish to further work up "hot" nodules on occasion, since there is a small chance (<1–2% at most) of malignancy in this type of nodule [15].

Thyroid Scanning in Patients with a Substernal Goiter

I-123 scintigraphy can be helpful in identifying large intrathoracic/mediastinal masses as functioning thyroid [80] thus differentiating these from other lesions such as lymphoma [67].

Whole-Body Scintigraphy in Patients with Thyroid Cancer

Diagnostic Whole-Body Scanning and Thyrogen Scanning

The application of most important nuclear medicine techniques in the follow-up and for delineation of treatment in patients with thyroid cancer is mainly represented by thyroid scintigraphy and whole-body iodine scintigraphy. The ATA guidelines allow clinicians to decide whether whole-body scanning is necessary prior to a therapeutic dose of I-131[27]. Some nuclear medicine departments use diagnostic scanning routinely and others almost never use it. I-123 is considered an optimal agent for diagnostic purposes before therapy with I-131; it may be a better initial diagnostic agent to be used or I-131 can be used for whole-body scanning prior to radioablation therapy [81]. I-123 is used for diagnostic whole-body scanning (acquiring images at 6, 24, 48 h after injection) in patients with DTC reducing the risk for "stunning" (a controversial phenomenon whereby a diagnostic dose of radioiodine, possibly I-131, may decrease uptake of a subsequent therapeutic dose by remnant thyroid tissue or by functioning metastases), and improving improves image quality because of its shorter half-life more favorable gamma energy [82]. In fact, for postablation follow-up, the use of I-131 doses of several mCi for scans can stun the thyrocytes and thyroid cancer cells [83, 84].

Low-iodine diet and a high-serum TSH (generally >25–30 μU/ml) are required for effective use of this technique [67]. Achieving high TSH serum levels slowly using thyroid hormone withdrawal can affect the patient's quality of life and at least theoretically may result in increased growth of metastatic thyroid tissue [85]. Recently, several clinical trials have proven that intramuscular injection of rhTSH (Thyrogen) is effective in achieving radioiodine uptake during nuclear scan imaging of thyroid cancer similar to a T4 withdrawal strategy thus allowing the patient to remain euthyroid during testing [85]. Most clinicians will have the patient stop T4 for a few days prior to scanning given the nonnegligible amount of iodine present in T4 preparations. One common standard protocol for using rhTSH in patients with thyroid cancer is the following: a single 0.9 mg (intramuscular injection) of rhTSH daily for two consecutive days (Monday and Tuesday); a dose of I-131 or I-123 is administered on the day after the second injection of rhTSH (Wednesday); a total body scan is performed 24–48h after radioiodine administration (Thursday or Friday); serum Tg detection is quantified 3–4 days after the second injection of rhTSH (Thursday and/or Friday) [85]; serum TSH may be assayed in order to verify that rhTSH has been injected. During this protocol a patient can continue to use thyroid hormone except for the few days prior to scanning. Anti-Tg antibodies must be assayed along with Tg to avoid false negatives due to antibody interference with the Tg measurement assay [51]. Anti-Tg antibodies will generally decrease and disappear in patients in complete remission [51]. rhTSH represents an important clinical tool to identify residual or metastatic thyroid tissue [85]. WBS findings (after rhTSH injection) must be correlated with serum Tg levels because different physiological and pathological conditions can result in misinterpreted WBS imaging results producing false positives that can be mistaken as metastases (Table 4.5) [67].

Table 4.5. Causes of false positives on whole-body scan radioiodide imaging misdiagnosed as metastasis from thyroid cancer

Physiological causes	Pathological causes
Salivary Glands	
Nasopharynx	Meningioma
Esophagus	Artificial eye
Thymus	Dacrocystitis
Breast	Parotid tumor
Stomach	Sinusitis
Liver	Dental caries
Gall Bladder	Tracheostomy
Intestine	Inflammatory lung disease
Urinary tract	Lung carcinoma
Contamination with saliva, stool or urine	Pleuropericardial cyst
	Struma cordis
	Hiatal hernia
	Zenker's diverticulum
	Barrett's esophagus
	Gastric adenocarcinoma
	Renal cyst
	Meckel's diverticulum
	Ovarian cystoadenoma

ATA management guidelines for patients with DTC propose that Tg unstimulated or stimulated levels greater than 2 ng/ml that increase over time may represent recurrent disease [27]. The presence of detectable Tg levels after total thyroidectomy and remnant ablation can be used to identify patients with persistent and recurrent disease (Fig. 4.6) [86]. I-131-WBS is also more sensitive after I-131 ablation of normal thyroid remnants because identification of neoplastic foci (which often have low radioiodine uptake) may be masked in the presence of thyroid remnants with a high uptake [86]. However, it is possible to obtain accurate Tg measurements for the follow-up of patients with DTC (after thyroidectomy) even without I-131 ablation treatment [86]. Serum Tg and diagnostic WBS have been considered complementary in identifying residual tumor for patients with a serum Tg below 1 ng/mL during thyroid hormone suppression [87, 88]. Undetectable levels of Tg with TSH stimulated (whether by thyroid hormone withdrawal or rhTSH) by itself may be all that is necessary in follow-up of patients at low risk for recurrence [87]. Diagnostic whole-body scanning (demonstrating functioning tissue, remnant, and/or metastasis, following thyroidectomy for DTC) can be performed by the absorbed radiation from 3 to 10 mCi (dose of I-131), causing suppression of iodine uptake function [81].

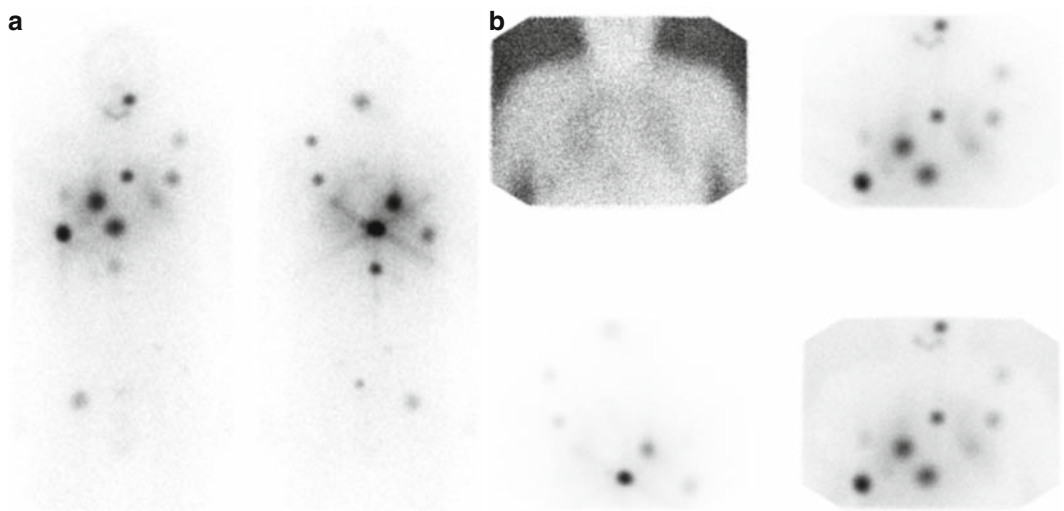

Fig. 4.6. Whole-body scanning with I-131 showing multiple foci of metastatic thyroid cancer throughout the body (**A**) and with detailed images of the patient's lungs (**B**).

PostTreatment Whole-Body Scans

Posttreatment whole-body scans are more sensitive than diagnostic whole-body scans; this phenomenon is related to much higher doses of I-131 used for treatment than for the diagnostic scans and helps detect additional metastatic foci in the bone, mediastinum, and lungs in approximately 10% of patients [89, 90]. Posttreatment WBS can show the lesions that produce Tg in patients with a negative diagnostic WBS for iodine uptake and detectable serum Tg levels [90, 91]. Posttreatment WBS generally is performed 5–7 days after treatment [67]. Posttreatment whole-body scanning allows the clinicians to tell whether any I-131 localizes into the malignant thyroid tissue and whether this agent will be helpful in future intervention (Fig. 4.6).

Use of Thyroid Scintigraphy in Congenital Thyroid Disorders

Congenital hypothyroidism (CH) (the overall incidence is 1 of 3,000–4,000 newborns) is related to developmental defects of the thyroid gland including agenesis, hypoplasia, and arrested migration of the embryonic thyroid cells. Other less-frequent causes of CH are functional thyroid cell defects, such as TSH resistance or dyshormonogenesis, alterations of secretion and action of thyrotropin-releasing hormone (TRH), and the action of T3 [92]. Work up of CH is based on clinical examination, biochemical tests, thyroid USS [93], and also on thyroid scintigraphy, using Tc-99m-pertechnetate or I-123 [94]. Imaging is centered on distinguishing between transient and permanent hypothyroidism [92]. Tc-99m pertechnetate is trapped, not organified, so thyroid uptake is similar to salivary uptake. Therefore, I-123 scintigraphy is preferable in the case of ectopic thyroid (usually a small sublingual gland) [94] Recently, it has been reported that rhTSH stimulation followed by I-123 thyroid scintigraphy can be used for diagnosis of CH during infancy [93].

Positron Emission Tomography

Patients with DTC that have a negative diagnostic WBS (by I-131 or I-123) and a negative head and neck ultrasound yet have detectable serum Tg need other diagnostic methods, such as positron emission tomography utilizing ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}FDG-PET). The use of ^{18}FDG-PET as the positron-emitting radiopharmaceutical has become increasingly common in the management of various malignancies of the head and neck [95]. This imaging technique is based on the principle that many malignancies metabolize glucose at a much higher rate than normal tissues. The images are made 1 h after injection of 10–20 mCi (370–740 MBq) ^{18}FDG. ^{18}FDG is converted in the cell to ^{18}FDG-6-PO_4 by hexokinase, similar to glucose. However, unlike glucose, which continues along the glycolytic pathway, ^{18}FDG-6-PO_4 cannot be metabolized any further, and thus accumulates in the cell. Tumor cells will accumulate more of this radioisotope, which can then be visualized during PET scanning. One limitation of PET scanning was the lack of anatomic information. More recently, imaging with ^{18}FDG-PET has been refined further with the introduction of a combined PET scan and computed tomography scans (PET/CT), where the PET images are fused with CT images. This is extremely important because PET/CT provides a detailed anatomic context for areas of increased uptake seen on PET scanning, allowing spatial localization of worrisome areas of increased metabolic activity [96] (Fig. 4.7). In order to supplement visual interpretation in PET exam, some investigators calculate a standardized uptake value (SUV) [also defined as the dose uptake ratio (DUR)] from the equation SUV $[T_{act}/V_{max}]/[D_{inj}/B]$; T_{act} is the tumor activity (in mCi or MBq), corrected for decay; V_{max} is the volume of tumor (in grams); D_{inj} is the injected dose (in mCi or MBq), and B is the body weight (in grams). If there is no excretion of activity and if the activity is uniformly distributed over the whole body, then the *SUV* is 1. In some cases an empirical value for SUV is selected, typically 2.0 ± 2.5, and lesions with values greater than that are considered to be malignant, but this has not yet been adapted to DTC. Currently both benign (chronic thyroiditis or benign nodules) and malignant thyroid lesions can have SUVs which are indistinguishable or at least overlapping.

More recently with the recognition of many "incidentally" detected thyroid nodules (Fig. 4.7) on PET imaging done for work up of other malignancies (such as lymphoma or lung

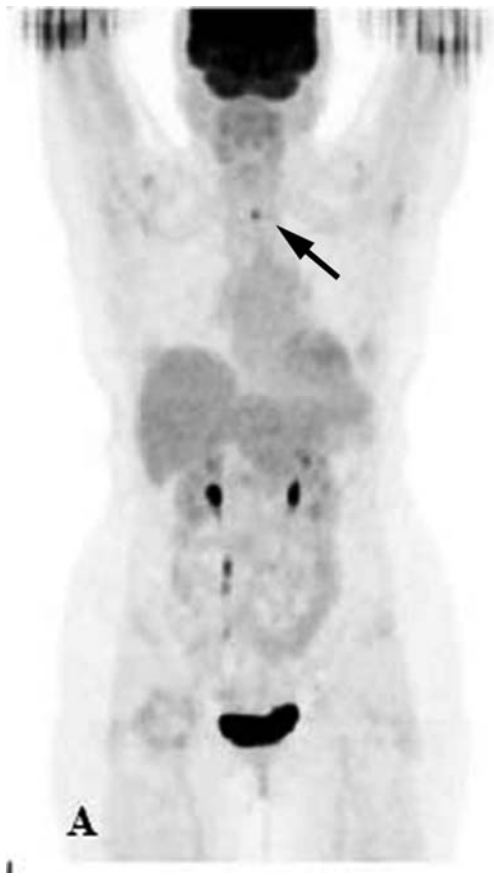

Fig. 4.7. PET/CT imaging of thyroid cancer. A small 7-mm incidentally detected papillary carcinoma in the thyroid marked by *black arrow*.

cancer) there has been some interest in whether ^{18}FDG-PET can be used to differentiate between benign and malignant thyroid lesions preoperatively, and consequently be used as a tool to select those who should undergo thyroidectomy. The results from these studies have shown that this imaging modality has the potential to be useful in differentiating benign from malignant lesions preoperatively showing a high negative predictive value for thyroid malignancy, especially in those patients with an indeterminate/microfollicular cytologic pattern on FNAB of the thyroid nodule [97–102]. In contrast, other findings were inconsistent with those of studies that have considered the usefulness of preoperative FDG-PET in the evaluation of cytologically indeterminate thyroid nodules for selecting patients for surgery because the glucose metabolic activities of benign thyroid follicular nodules were as high as those of malignant nodules [103]. Studies examining the usefulness of FDG-PET in differentiating malignant from benign nodules have reported conflicting results; most found considerable overlap in glucose metabolic activities between malignant and benign nodules [97, 99, 100, 102, 104]. Careful selection of patients who could most benefit from the additional information this test provides will be crucial and additional studies with larger sample sizes need to be performed to clearly establish the true efficacy and utility of this test in the preoperative management of thyroid nodules.

PET/CT has mainly been used for postoperative surveillance of patients with known thyroid cancer, especially those with poor differentiation or negative WBS despite Tg positivity [95, 105–107]. Poorly differentiated or dedifferentiated thyroid carcinomas have more limited abilities to concentrate radioiodine, leading to negative I-131 scans despite significant increases in thyroglobulin. However, these poorly differentiated lesions tend to be more metabolically active, and therefore take up ^{18}FDG which can be visualized during PET scanning [95, 105, 108] (Fig. 4.8). If the extent of disease recurrence can be identified in these patients with PET/CT then surgical excision or other therapeutic interventions may become possible.

Computed Tomography Scan and Thyroid Imaging

CT is occasionally used for the diagnosis of thyroid disorders [24], though it is not able to distinguish benign nodules from carcinoma [24]. CT is better than USS for evaluating the mediastinal extension of thyroid masses [24], and is also very accurate to evaluate the spread of thyroid carcinoma, especially into certain lymph node basins or in patients with local invasion of adjacent structures. CT has some limitations such as cost, artifacts caused by swallowing or breathing, difficulty with foreign objects such as metal scatter from surgical clips and exposure to ionizing irradiation [24, 109, 110]. Density value is quantified in CT numbers and the Hounsfield scale (HU) is a quantitative scale for describing radiodensity. Sometimes contrast materials such as

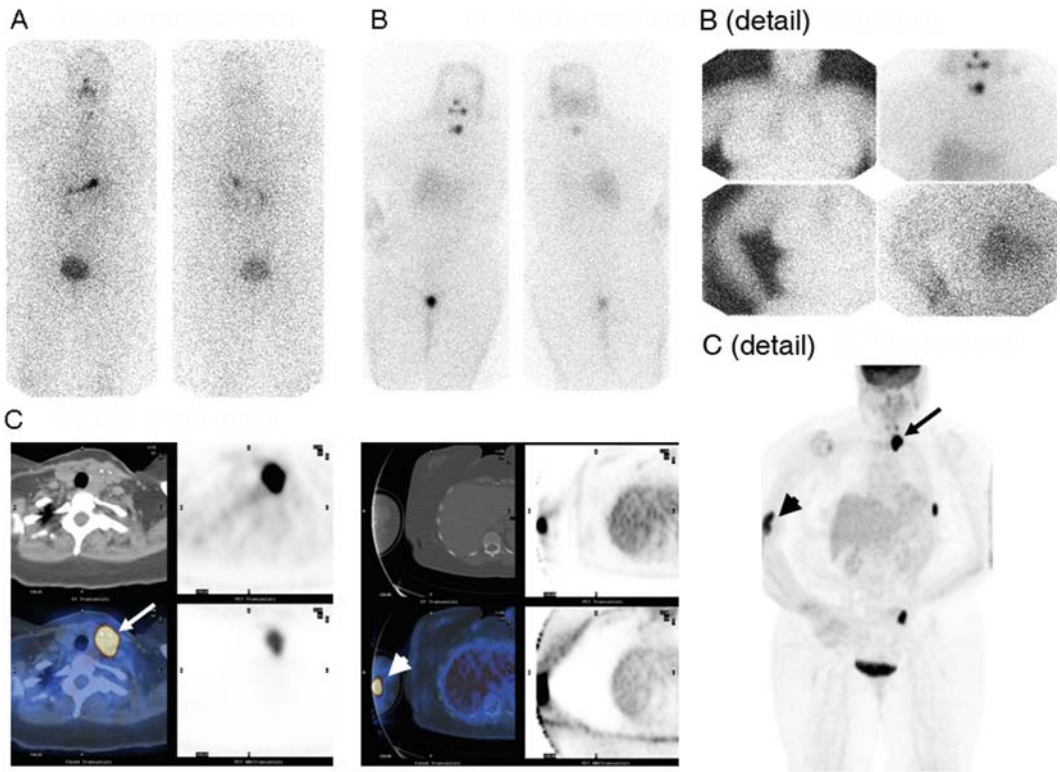

Fig. 4.8. Utility of PET/CT scanning in patients with non-I-131 avid disease. (**A**) I-123 diagnostic scan in patient with a fractured *right* humerus suspicious for metastatic Hurthle cell thyroid cancer shows no uptake in thyroid bed or humerus. (**B**) Posttherapy scan after administration of I-131 shows some uptake in thyroid only. (**C**) PET/CT images with detail shows intense uptake in *left* thyroid bed (*arrow*), *right* humerus (*arrowhead*), and *left* ribs.

intravenous iodinated contrast are used. This is useful to highlight structures such as blood vessels that otherwise would be difficult to delineate from their surroundings. CT with contrast should not be used in patients who may need treatment with radioiodine within a few months since the iodine load reduces the iodine uptake of any thyroid tissues for 8 weeks or longer. Moreover, it has been reported that in normal thyroid tissues without calcifications CT density values correlate linearly with iodine concentration [111] and based on this demonstration, the decrease in CT values not only could reveal a reduction of iodine concentration in the thyroid follicles but also represent a decrease in follicular content and subsequently an increase of follicular cells [112].

Seventy-five to eighty percent of retrosternal goiters have an extension in the anterior mediastinum and 20–25% in the posterior mediastinum [24]. In addition, CT can provide anatomical informations such as compression of the trachea, esophagus, and great vessels [113]. Features of substernal thyroid gland include anatomic continuity with the cervical thyroid, focal calcifications, relatively high CT number, rise in CT number after administration of iodinated contrast material, and prolonged enhancement after contrast material administration. However, these features are not always observed in patients with intrathoracic goiter but a combination of these should be accurate to have an appropriate diagnosis [114].

CT can be used in the follow-up of patients with thyroid carcinoma as useful adjuvant imaging method to detect loco-regional recurrence of thyroid carcinoma in the neck and/or metastases [115]. Pathognomonic signs of metastatic lymph nodes can be recognized by size, shape, and/or presence of nonenhancing areas after contrast medium injection. This latter

phenomenon may be due to tumour necrosis, tumour keratinization, or cystic areas inside the tumor [116]. In patients with thyroid cancer, mediastinal lymph-node metastases are often associated with lung metastases and the preoperative localization with CT with injection of contrast medium is an important diagnostic phase and should be realized six weeks before any administration of I-131 [115]. CT is elective in the diagnosis of the aero-digestive tract invasion from thyroid carcinoma [115]. Finally, it is also helpful in the identification of hepatic metastases from medullary thyroid carcinoma [24].

CT shows a hypodensity in nonautoimmune nontoxic diffuse goiters with a homogeneous enlargement of thyroid gland. In Graves' disease and autoimmune thyroiditis is reported a hypodensity of thyroid gland on CT [117]. On CT scan, primary thyroid lymphoma should be included in the differential diagnosis when a homogeneous thyroidal mass is seen isoattenuating to muscles, with a strong tendency to compress normal remnant thyroid and the surrounding structures without invasion [118].

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5

Multinodular Goiter

Abdullah N. Hisham

Introduction

Goiter is a general definition of any enlargement of the thyroid gland; multinodular goiter is the name given where multiple nodular enlargements have developed within the thyroid gland. David Marine was the first to postulate the formation of multinodular goiter, which is caused by inadequate production of thyroid hormones coupled with the increase in thyroid-stimulating hormone (TSH) response. This led to the initial phase of hyperplastic changes in the thyroid gland. Subsequently, when there is iodide repletion or decreased requirement of thyroid hormone, the thyroid gland responded into a resting phase of colloid storage. It is the repetition of these two phases of the cycle that would eventually lead to formation of multinodular goiter [1]. Selwyn Taylor supported this concept and believed that the initial formation is diffuse thyroid hyperplasia, but with time discrete nodules develop [2].

Multinodular goiter is the most common thyroid disorder worldwide. The prevalence of multinodular goiter varies according to geographical regions; it is estimated that 4–5% of the normal female population over the age of 50 has a palpable multinodular goiter [3]. The prevalence is much higher when ultrasonography is used to detect multinodular goiter [4]. Multinodular goiter may be endemic or sporadic in origin. Endemic goiters are mainly attributed to iodine deficiency in the dietary intake and lack of exogenous iodine supplementation. By and large, in iodine-sufficient countries the prevalence of goiter is not higher than 4% [5]. On the other hand, the prevalence of endemic goiter is much higher in iodine-deficient countries, estimated to be 15% in mild and 22.6% in moderate iodine-deficient regions. The increase in the size of goiter is in parallel with the severity of iodine deficiency [6]. Overall it has been estimated that over 12% of the world's population live in iodine-deficient regions. In Malaysia at least 7% of the population is at risk of developing endemic goiter, particularly aborigines and Malays in remote inland areas and natives living in Borneo (in Sabah and Sarawak) away from the seacoast [7].

On the other hand, sporadic goiters may be attributed to the endogenous factors and defect in thyroid hormone synthesis. Goitrogenic substances in the diet and certain medications such as lithium, sulfonamides, and aminoglutethimide have been implicated to cause a prolonged fall in serum T4 levels, which led to the feedback response of high TSH levels to the thyroid glands [8]. Both endemic and sporadic goiters are caused by increased TSH response due to low thyroid hormone production. Sporadic goiter, which is also known as nonendemic goiter or colloid goiter, occurs in about 5% of population for which there is no apparent cause found. It was earlier hypothesized that sporadic goiter was due to prolonged

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physiological stimulation from the mildly elevated TSH level, which was undetected. Another possible explanation is the radiation exposure to the head and neck during childhood, which increases the risk of not only malignant nodules but also benign multinodular goiter. Nevertheless, in most instances no specific cause is identified, although a defect in genetic makeup has been suggested [9, 10]. Multinodular goiter is the most common thyroid disorder, with a wide spectrum of clinical presentation and severity. Most goiters are discovered incidentally and are asymptomatic at presentation. They are slow growing and may cause only little discomfort. Subtle forms of symptoms may go unnoticed for many years and not infrequently patients may only be aware of a dominant multinodular goiter, which present as a single palpable nodule. Conversely, large and massive goiters continue to exist in iodine-deficient regions, particularly in the developing countries. Large goiters in the neck not only affect the cosmetic appearance, but lead to predominant signs and symptoms that are closely related to the enlarging mass, impinging onto the adjacent structures and causing significant compressive symptoms of dysphagia, dyspnea, choking sensation, or even hoarseness of voice.

Further downward growth of a goiter occurs in the path of least resistance into the thoracic inlet forming a substernal goiter. Most substernal goiters are asymptomatic and detected only on routine medical examination with chest radiograph. However, large substernal goiters may present with symptoms of chest discomfort and significant obstruction to the venous return. The venous obstruction of the jugular veins may be made apparent by having the patient elevate the arms above the head, indicating a positive Pemberton's sign. Not infrequently the compressive symptoms with chest discomfort may be misinterpreted as cardiopulmonary symptoms. Once detected there is an urgent need for intervention as any sudden glandular bleeding may exacerbate the compressive symptoms, leading to life-threatening emergency. Other reasons for removal are suspicion of malignancy and prevention of future complications. Although the majority of multinodular goiters are in euthyroid state, hyperfunctioning or rarely hypofunctioning has been reported.

Embryology and Surgical Anatomy of Thyroid Gland

The practice of thyroid surgery should always be based on a thorough understanding of the embryology and surgical anatomy. It is imperative for surgeons to appreciate the anatomical planes, enlargement variations, and abnormalities in relation to the surrounding structures to map for the best options of safe surgical approach. The thyroid gland develops from the median endodermal thickening in the floor of the primitive pharynx. This thickening invaginates from the foramen cecum with a downward growth and descends passing ventral to the developing hyoid bone and laryngeal cartilages. At this stage, the developing median thyroid gland is connected to the tongue by the thyroglossal duct. The pyramidal lobe is formed from the remnant of the distal end of thyroglossal duct. The median thyroid lobe continues to divide into two medial thyroid lobes connected by the isthmus. Here the thyroid gland acquires the shape of a butterfly and resides anterior to the second and third tracheal rings. Most would not appreciate the presence of the lateral thyroid lobe, also known as the posterior horn of thyroid gland, which arises from the fourth branchial cleft and ultimobranchial body on both sides. The lateral lobes develop from the ectodermal origin, which is rich in parafollicular cells, and later fuse with the medial thyroid lobes to form the thyroid gland [11]. This fusion of the thyroid's C cells is closely associated with other ectodermal endocrinopathy such as in MEN 2A. It is not surprising to learn that as a result of the incomplete fusion of the lateral and medial lobes, a tubercle with higher concentration of calcitonin is formed. The tubercle was named after Emil Zuckerkandl, who described this incomplete fusion back in 1902 [12]. The importance of the Zuckerkandl tubercle when present is that, if not appreciated and removed during thyroid surgery, it may be a persistent source of unrelieved compression symptoms and remnant for future recurrence [13]. Furthermore the understanding of the anatomy of Zuckerkandl's tubercle is important as a guide to safe dissection. The tubercle enlarges laterally and above the recurrent laryngeal nerve, forming a medial cleft, and at this point of dissection, it

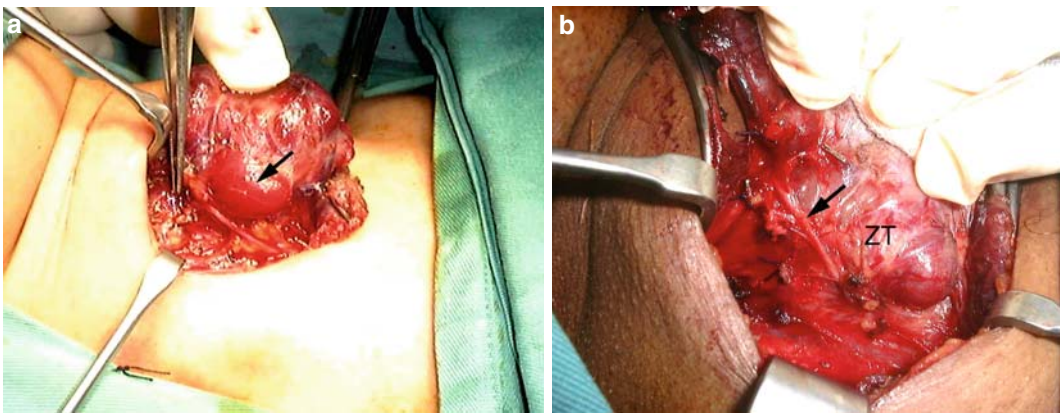

Fig. 5.1. (**A**) Early exposure and elevation of the Zuckerkandl's tubercle (*arrow*) invariably will allow the recurrent laryngeal nerve to be easily and safely encountered. (**B**) The uncommon variation where the recurrent laryngeal nerve (*arrow*) runs lateral and lying on the Zuckerkandl's tubercle (ZT).

may appear as if the recurrent laryngeal nerve is passing directly into the thyroid gland. Hence early exposure and elevation of the Zuckerkandl's tubercle will invariably allow the recurrent laryngeal nerve to be easily and safely encountered. This is an important constant anatomical landmark to encounter the recurrent laryngeal nerve (Fig. 5.1A) [14, 15]. A unique feature is the uncommon abnormal variation where the recurrent laryngeal nerve runs lateral and lies anterior on the enlarged Zuckerkandl's tubercle, thus to some extent placing it at increased risk of damage during dissection (Fig. 5.1B) [16].

Special care should be taken to avoid undue traction and dislocation of the tubercle before the nerve is encountered. Another important point is that the normal superior parathyroid gland, also being derived from the fourth branchial cleft, is commonly found in close association, cephalad to the tubercle [11, 14–16]. The presence of Zuckerkandl's tubercle is frequently recognized only when full mobilization of the respective lobe has been achieved [15, 16]. When the tubercle is obvious particularly when it is more than 1 cm in size, it is noted to be associated with 81% of appreciable compressive symptoms from either the enlarged retrotracheal or the retro-esophageal extension [13, 16]. The significance of the compressive symptoms due to the size of the tubercle is well recognized, but perhaps more important is the location of the tubercle from either a retro-tracheal or a retro-esophageal extension regardless of the size of goiter. It is possible that the embryological formation of the tubercle continues to enlarge over a period of time caused by hyperplastic or neoplastic changes as postulated in the formation of multinodular goiter (Fig. 5.1). More often than not, all large goiters are significantly associated with the increase in the size of the tubercle [13]. Pelizzo et al. proposed a classification based on the size of the tubercle and its fusion with the principal medial thyroid lobe. The classification proposed was grade 0 – unrecognizable, grade 1 – only a thickening of the lateral edge of the thyroid gland, grade 2 – smaller than 1 cm, and grade 3 – larger than 1 cm [14].

The Zuckerkandl's tubercle is an important anatomical landmark commonly found in large multinodular goiter, which has a sound embryological basis with significant clinical implications. The value of preoperative lateral neck radiograph to detect the enlarged tubercle is substantiated with the widening of retro-visceral or prevertebral soft tissue measurement at C4, C5, and C6 levels (Fig. 5.2A). It would seem that the C4 level is the most promising predictor of enlarged Zuckerkandl's tubercle and any widening of 16.5 mm or more observed in the lateral neck radiograph has 100% specificity to diagnose the enlarged grade 3 tubercle [17].

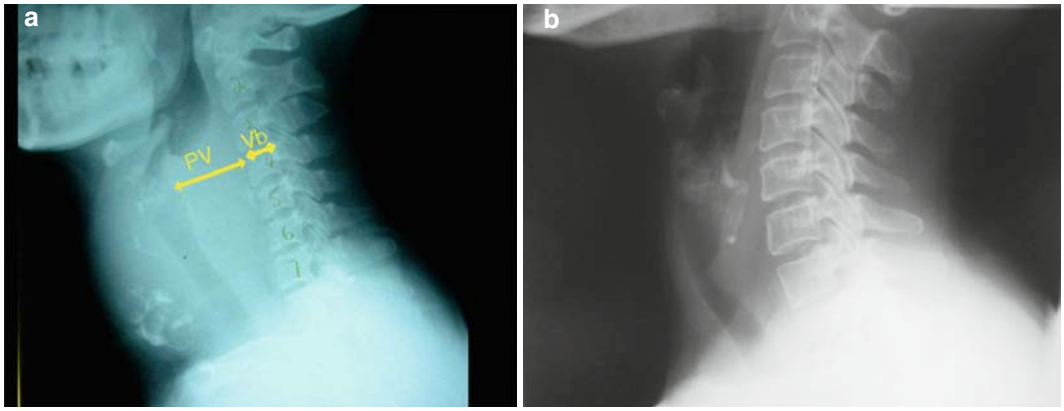

Fig. 5.2. (**A**) The widening of retro-visceral or prevertebral soft tissue measurement at C4 level is the most promising predictor of enlarged Zuckerkandl's tubercle. (**B**) Lateral radiograph showing direct posterior compression narrowing the airway with severe symptoms of dyspnea, stridor, and dysphagia.

Clinical Presentation of Multinodular Goiter

The signs and symptoms of multinodular goiter are predominantly related to the enlarging mass leading to significant compression and impingement onto the local adjacent structures. To some extent, the location and extension of the goiter may be more crucial than its absolute size to cause compressive symptoms as has been described earlier. The compressed trachea or esophagus or both may result in common symptoms of dysphagia, dyspnea, coking sensation, or stridor, made worse when patient is in recumbent position. On the contrary when there is hoarseness of voice, a presumptive diagnosis of malignant goiter with infiltration into the recurrent laryngeal nerve must be considered, as rarely it may occur from enlarging mass stretching on the nerve. Similarly Horner's syndrome as a result of local pressure on the sympathetic ganglions and nerves is a rare occurrence.

There is numerous definition and classification proposed to categorize thyroid enlargement. Large goiter has been defined as a protrusion beyond the chin or jaw, and according to the World Health Organization classification, large goiter is a stage 3 goiter visible from a distance of several meters. Stage 1 is where the thyroid enlargement is not visible but palpable and Stage 2 is where the thyroid enlargement is clearly visible on close inspection. Perez classification of large goiter is when a goiter weighs 80 g or more after excision or has the largest neck circumference crossing the goiter being 40 cm or more [18].

Large goiters are common in iodine-deficient regions and although long-standing large goiter in the neck is clinically apparent with cosmetic problems, it appears to be tolerated by many patients in endemic regions. Surgery is inevitable in those with large goiter with significant compressive symptoms. The effects of compression onto the vital structures and distortion of the anatomy increase the difficulties of surgery and pose a unique challenge to surgeons. It is clear that unilateral dominant goiter with lateral compression can displace the hyoid, trachea, and larynx to the contralateral side. However, in bilateral nodular enlargement, lateral compression on both sides of the trachea and larynx may cause a critical narrowed slit airway. In such circumstances horizontal finger pressure maneuvers by the patient anterior to the trachea may help a little to temporarily ease the airway. Direct posterior compression from the retro-tracheal or retro-esophageal extension may also cause significant compression symptoms as seen in the lateral radiograph (Fig. 5.2B).

Thyroid enlargement descending lateral and posterior into the narrow thoracic inlet may cause considerable neck discomfort and the sensation of tightness. The downward growth is often restricted anteriorly by the pretracheal muscles, which are inserted into the posterior

part of the clavicle and sternum. Nonetheless the rare entity of presternal extension in the midline has been reported [19]. The continuation of downward growth of a goiter below the level of the manubrial notch and thoracic inlet may be drawn by the process of swallowing and increased in the negative thoracic pressure. The lower pole is the usual starting point of a growth to descend, but occasionally the growth may start from a lateral lobe. Initially the thyroid enlargement moves in and out of the thorax with swallowing, and further downward prolongation would require an increasing thoracic pressure upon coughing to plunge the mass out of the thorax. This plunging goiter is easily removed through a cervical approach. As more and more mass volume forms and with further downward growth, the goiter reaches a size that precludes its movement out of the thorax. Various stages of downward growth have been proposed to describe the process of descend [20]. A stage 3 goiter is where only a fibrous band attaches to the goiter and stage 4, a complete isolated mediastinal goiter disconnected from the principal thyroid gland in the neck [20]. Such isolated substernal goiter adds to the difficulties in diagnosis and invariably may resort to a sternal split for removal.

Diagnostic Modalities

All patients diagnosed with multinodular goiter must be screened for thyroid function to determine the serum level of free thyroxine (T4) and TSH levels. Imaging studies are useful to assess the extent of displacement and constriction of the trachea and esophagus. A chest radiograph is a simple investigation that will often show deviation of the trachea and the presence of a substernal tumor. Although trachea displacement and compression is frequently documented in most cases this is rarely critical to warrant emergency surgery. Lateral chest radiography may be helpful to detect posterior compression and presence of enlarged Zuckerkandl tubercle. Barium studies may demonstrate clearly the indention of the esophagus from the posterior or the lateral side. Ultrasound is an important and noninvasive bedside imaging study, which is now increasingly being accepted as part of the armamentarium of endocrine surgeons. Not only important information of the size, number, and location of the nodules can be measured but also important adjacent structures to any local compression. Computer tomography and magnetic resonance imaging provide additional information on the location and extension of the goiter. Both are highly accurate to detect the severity of tracheal or venous compression and help to categorize the substernal goiter with best possible of approach for surgery. Furthermore both imaging studies may be necessary to distinguish a goiter from a vascular tumor or aneurysm. Radioisotope scanning is helpful in defining the limits as well as in identifying the nature of the mass. Flexible laryngoscopy is a routine assessment for all patients undergoing surgery in particularly those patients with voice changes and for reoperative surgery. Thyroid scan is a useful preoperative assessment particularly to confirm isolated substernal goiter from other mediastinal mass. Malignancy should be considered in longstanding multinodular goiter when there is sudden enlargement within a dominant nodule, hoarseness of voice, presence of lymph nodes coupled with past history of neck irradiation particularly in childhood. The fine-needle aspiration may be helpful in multinodular particularly if suspicious of malignancy in a dominant nodule. It has been reported that 4–17% of multinodular removed at operation were found to harbor malignancy [21–23]. This high incidence rate may be unduly influenced by diagnostic and selection bias in surgery. It is likely that the surgery was performed in patients diagnosed with multinodular goiter with high suspicion of malignancy. Fortunately most are low-grade thyroid cancers and are typical of the papillary variety and not clinically active. Samson reported 17% of small papillary carcinomas of the thyroid gland in routine autopsies of patients not known to have any thyroid disease or past irradiation [24]. At this stage it is not certain whether these lesions noted in autopsies would show any overt clinical evidence of malignancy.

Therapeutic Options

Iodine prophylaxis via the dietary intake of iodized salt is the most effective means of prevention and treatment for endemic goiters. Treatment for multinodular goiter is indicated

when there is presence of local compression symptoms, rapid enlargement in short period of time, suspicious or proven malignancy, and cosmetic consideration. No medical or surgical treatment is necessary if the goiter is asymptomatic and not growing in size. Although levothyroxine therapy has been widely used to shrink and arrest further growth of nodular goiter, there is little evidence to support its efficacy and the benefit is limited [24, 25]. However, some would still favor this suppressive therapy, but it should only be reserved for younger patients with early small nodules [26].

Over the years radioiodine therapy is increasingly being considered in the treatment of multinodular goiter, and it offers an alternative strategy to surgery. Radioiodine therapy has intriguingly shown consistent results of volume reduction from 35 to 40% in the first year and from 40 to 60% in the second year of treatment with minimal side effects [27, 28]. More recently the application of recombinant human thyrotropin has demonstrated to increase the uptake of radioactive iodine (RAI) and enhanced the effect of radioactive iodine therapy [28–30]. On the other hand, it is clear that the enhancement effect has implication of an increased risk for developing hypothyroidism [29, 30]. The introduction of fractionated radioiodine therapy in large nontoxic goiter has been reported with success [30]. So far there is growing interest to expand the indication for radioiodine therapy not only to those with small goiters, elderly with comorbidities, or those patients with substantial risk of surgery, but also to those with large goiters and who opted for nonsurgical approach. Given the benefit of doubt, there is a clear need for ongoing prospective randomized data with long-term outcome to substantiate the routine application radioiodine therapy in the management of multinodular goiters.

Although the renewed interest in multimodality treatment of multinodular goiter has been made available, surgery remains to be the first choice of treatment. The main indications for surgery are for suspected or proven malignancy, effects of local compressive symptoms, those with large and substernal goiters. The surgical options for the management of multinodular goiter include bilateral subtotal thyroidectomy, subtotal resection with contralateral lobectomy, or total thyroidectomy. At present total thyroidectomy is the preferred option for the management of benign multinodular goiter [31–33]. Total thyroidectomy is an appropriate surgical procedure when both lobes are involved. It avoids further surgery in cases of proven malignancy and prevents any possibilities of future recurrence. The argument against total thyroidectomy for a less-extensive procedure is based on the fear of excessive morbidity to the laryngeal nerves and parathyroid glands. It was reported that total thyroidectomy is associated with an increased rate of recurrent laryngeal nerve palsies and hypoparathyroidism in comparison with less-extensive surgery [34]. On the contrary total thyroidectomy is increasingly being accepted as the choice of surgery for multinodular goiter provided if it could be done safely with minimal morbidity to the laryngeal nerves and the parathyroid glands. All efforts should be made to preserve the parathyroid glands during surgery, but if this is not possible parathyroid autotransplantation of at least one gland should be made to reduce the incidence of hypoparathyroidism [35]. The potential benefits of total thyroidectomy relate to complete removal of the disease and prevent reoperative surgery for recurrence disease, which indeed carries a higher risk and morbidity [36, 37]. Conversely hemithyroidectomy is adequate for removal of dominant multinodular goiter involving one lobe of the thyroid gland [38]. Although the incidence of tracheomalacia has been reported to range from 0.001 to 1.5% this complication remains a rarity [39]. It is more likely to occur in those patients with long-standing large benign goiters. In such a situation, the sensible decision is to perform a tracheostomy at the end of the surgery [40].

Substernal Goiter

In 1749, Haler was the first to describe a comprehensive account of substernal goiter [41], and the first successful surgery for substernal goiter was performed by Klein in 1820 [42]. The reported incidence of substernal goiter in the general population varies from 0.02 to 0.5% based on all chest radiograph-screening reports [43]. Substernal goiter has been reported to range from 1 to 15% of all thyroid surgery and accounts for about 5% of all mediastinal mass removed at thoracotomy [44, 45]. The definition

of substernal goiter has not been uniformly standardized and accepted [46]. Substernal goiter was defined as a lesion of the thyroid gland extending to the fourth thoracic vertebra on chest radiograph [46], or extending down to the aortic arch [47]. Hedayati and Mc Henry literally consider every thyroid that extends below the manubrium as substernal goiter [48]. Lahey's definition of substernal goiter is where the greatest diameter of the thoracic mass by roentgenogram is well below the thoracic inlet [49]. A popular view and the most widely applied definition of substernal goiter was described by Katlic, where more than 50% of the thyroid gland is below the suprasternal notch [50].

Zylak proposed a system to categorize the mediastinum with computerized tomography scan. The mediastinum is being divided into three longitudinal compartments extending from the level of the thoracic inlet to the diaphragm [51]. The middle mediastinal compartment is exclusively a vascular space that incorporates the pericardium and its contents, the great veins, and the anterior aorta and its major branches. The anterior mediastinal compartment is bounded anteriorly by the sternum and posteriorly by the middle mediastinal and contains the thymus. The posterior mediastinal compartment is bounded anteriorly by the pericardium and great vessels, posteriorly by the prevertebral fascia and anterior longitudinal ligaments, and laterally by the respective parietal pleura. It contains the esophagus, descending aorta, azygos and hemiazygos veins, thoracic duct, lymph nodes, and neural structures [51]. The growth of a mediastinal goiter along the path of least resistance is delineated by the anatomic constraints in a confined space.

Classification of Substernal Goiter

Substernal goiters are classified as either primary or secondary. Primary or isolated substernal goiter is totally confined to the thoracic cavity and in most instances remains asymptomatic and undetected. Less than 1% of goiters are truly isolated in the thorax, and it is believed that the primary substernal goiter is congenital in nature and arises from aberrant thyroid tissue. In majority of cases isolated substernal goiters are totally without any connection with the cervical thyroid gland and reside in the anterior mediastinum. Isolated anterior substernal goiters have their own blood supply derived from the nonanatomic mediastinal vessels. On the other hand isolated posterior substernal goiters are extremely very rare and only few cases have ever been described in literature [52]. Secondary substernal goiter is presumed to originate from the embryological descent of the thyro-thymic tissue and continues growth downward along the plane of the cervical and mediastinal fascia. Here the blood supply derives principally from the inferior thyroid arteries and venous return is through the inferior thyroid veins. Most substernal goiters are of secondary goiters and descend into the anterior mediastinal compartment. Numerous classifications of substernal goiters have been introduced, but there is lack of general consensus to categorize them systematically. It is certainly important to classify substernal goiter in relation to the surrounding structures as it could offer vital clinical information and best possible options of safe surgical intervention. Higgins' classification includes substernal, partially intrathoracic, and completely intrathoracic based on the percentage of neck versus intrathoracic disease [53]. Cohen and Cho classified the goiter based on the percentage of mediastinal component of substernal goiter; grade 1 indicates 25% or less of the goiter is in the mediastinum, whereas grade 2 is between 26 and 50%. Grade 3 implies 51–75% and grade 4, more than 75% of the goiter is in the mediastinum [54]. Perhaps the most useful in the clinical practice is the anatomic classification proposed by Shahian based on the mediastinal compartment and either a primary or a secondary goiter [55]. It gave a comprehensive illustration of the contralateral posterior mediastinal goiter with either a retro-tracheal or a retro-esophageal extension.

Given the difficulties that may be encountered during the surgery, first it is important to define the lower end of substernal goiters, which may be located well below the level of aortic arch and as far down to the diaphragm. Second it is equally important to learn the direction of growth and impingement onto any vital structures, and third it may require a proper strategy and a careful assessment for the best route of surgical approach for safe resection. We proposed a classification of substernal goiter based on the Zylak's division of

Table 5.1. Classification of substernal goiter

Type	Subtype	Description	Operative approach
Anterior	A I	isolated	Sternal split
	AII	substernal extension	Collar ± Sternal split
	AIIIA	crossed-over **anterior**	Collar ± Sternal split
	AIIIB	crossed-over **posterior**	Collar and Sternal split
Posterior(Back)	B I	Isolated	Thoracotomy
	BII	Substernal extension	Collar ± thoracotomy
	BIIIA	Crossed-over **anterior**	Collar ± thoracotomy
	BIIIB	Crossed-over **posterior**	Collar ± thoracotomy
	1	Retro-tracheal extension	
	2	Retro-esophageal extension	

Abbreviation: A: anterior, B: posterior (back).

the mediastinum into three longitudinal compartments. This classification not only takes into account the anatomic compartment but also the possible variation of substernal goiters growing in the mediastinum coupled with the best possible surgical approach (Table 5.1).

It is clear that in a confined space the substernal goiters frequently compressed onto the trachea and the large veins, and to some extent causing critical narrowed airway, venous engorgement, and even superior vena cava obstruction. Fortunately most anterior substernal can be removed entirely through a cervical approach with a low complication rate. The anterior crossed-over substernal goiter to the opposite side is rather unique in the sense that it descends downward and crosses over from the right to the left side (Fig. 5.3) or vice versa. One quarter of mediastinal goiters are in the posterior mediastinum. It arises from the posterior and lateral aspects of the thyroid gland in the neck and descends into the thorax. Two thirds of the posterior mediastinal goiter exclusively occur on the right side [55]. This is due to the position of the aortic arch and descending aorta, which occupies the left side of the thorax, and thus preventing the goiter from descending on the left side. Contralateral or crossed-over substernal goiter is a rare clinical entity in the posterior mediastinum. Often the crossed over is part of the extension from left-sided gland to the right side of the posterior mediastinum either crossing behind the esophagus or sandwiched between the trachea and the esophagus (Fig. 5.4).

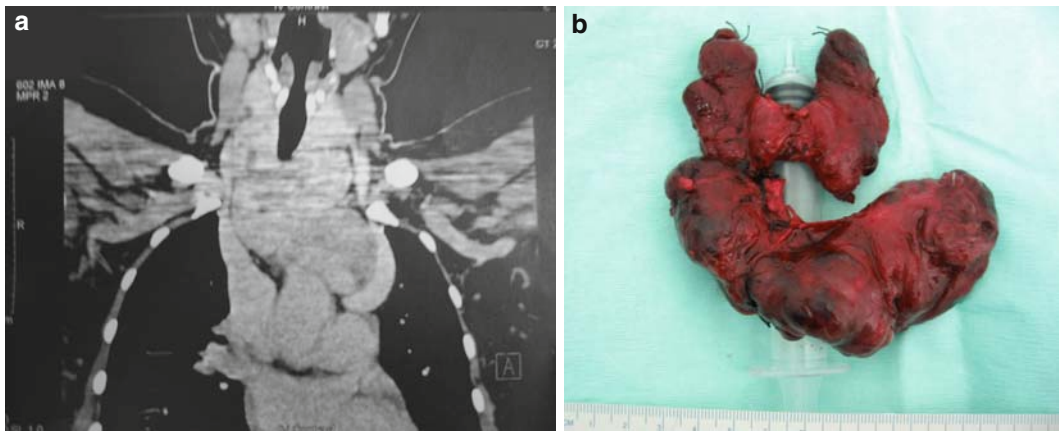

Fig. 5.3. CT scan (**A**) and gross specimen (**B**) showing the anterior crossed-over substernal goiter from the right to the left side.

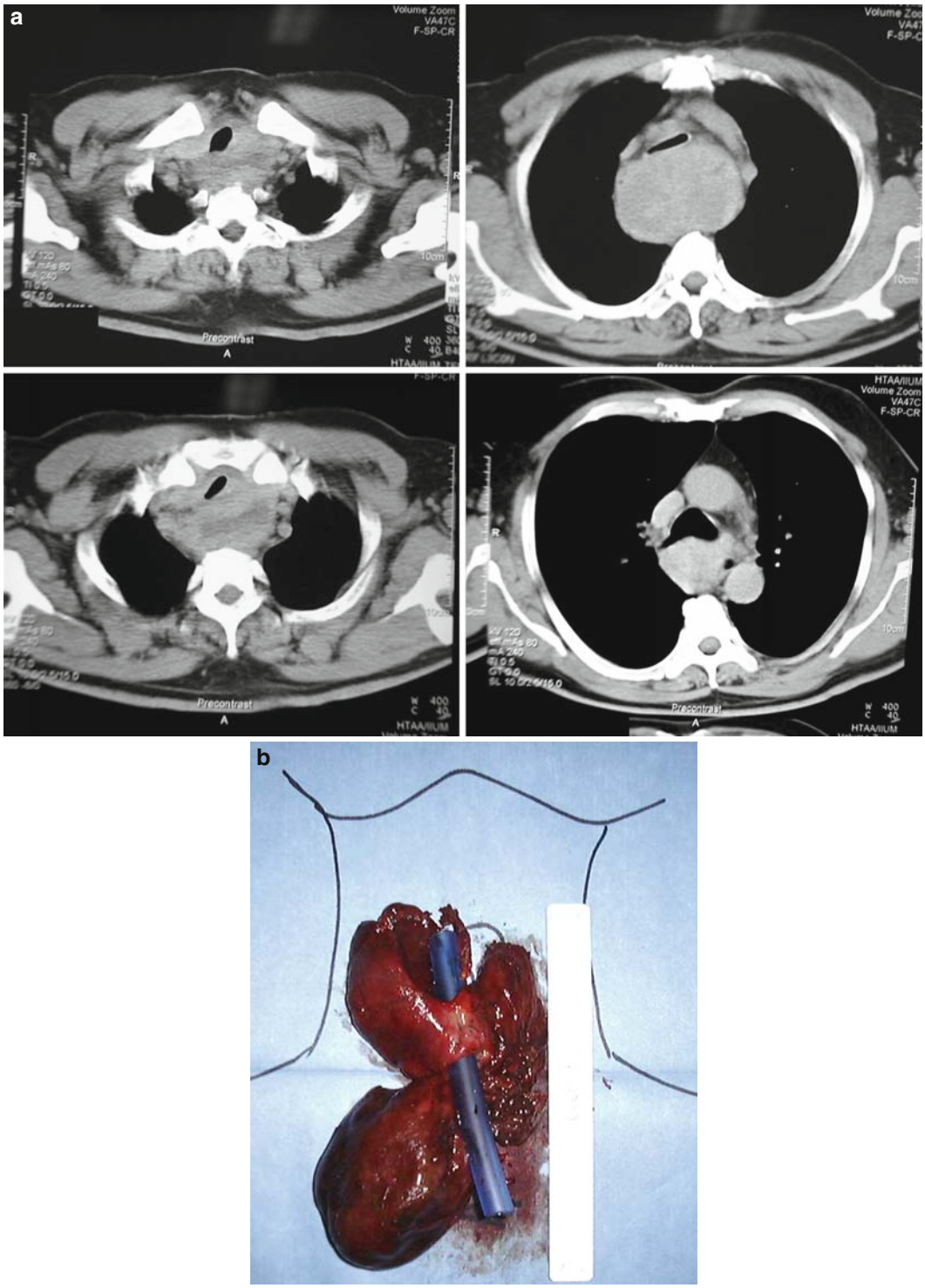

Fig. 5.4. (**A**) CT scan showing the crossed-over posterior substernal goiter extending below the level of carina. (**B**) A large gross specimen of the crossed-over posterior substernal goiter completely removed through the collar incision using Lahey's technique.

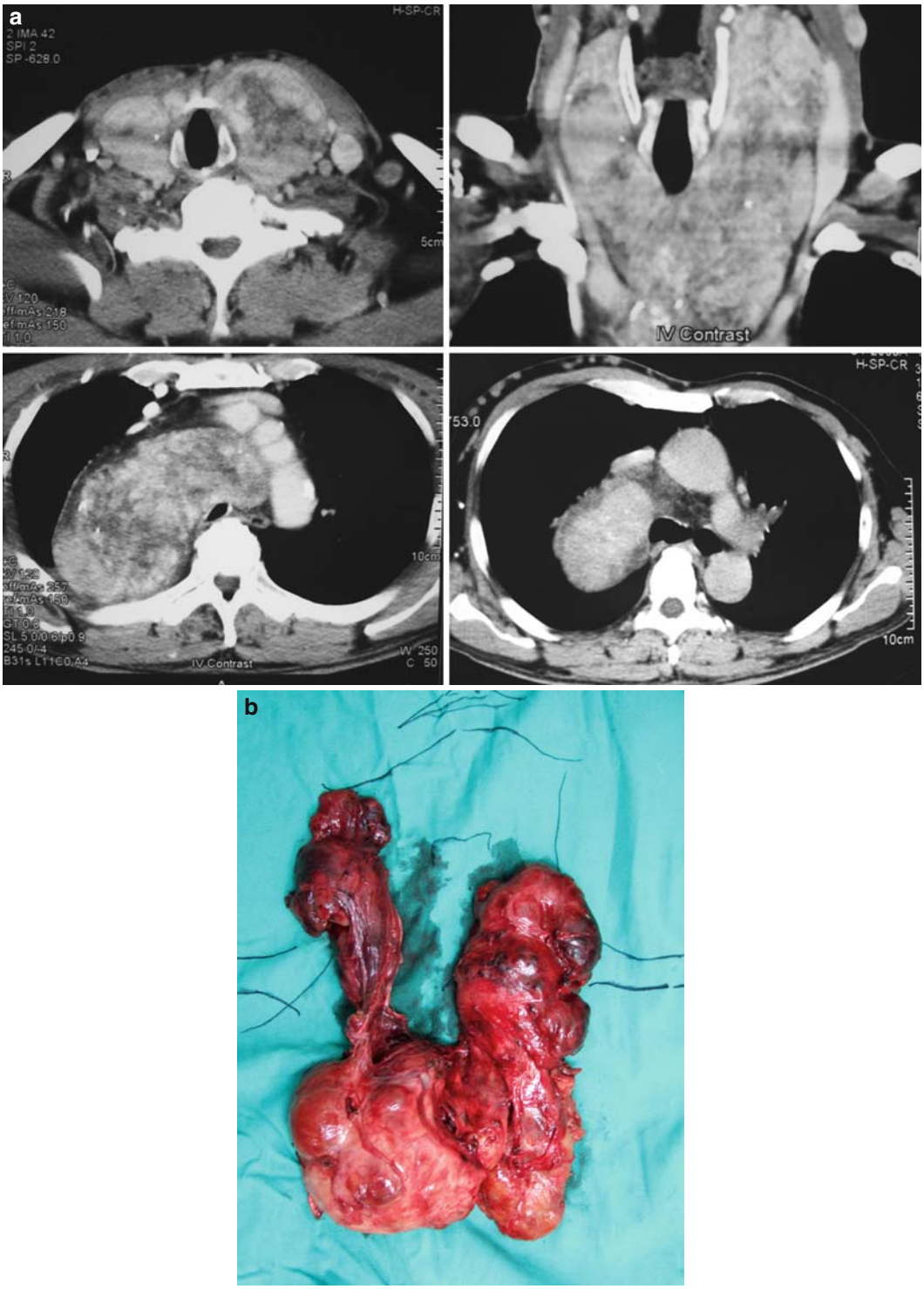

Fig. 5.5. (**A**) The anterior substernal goiter crossed over the aortic arch to the opposite right side of the posterior thorax. (**B**) Gross specimen of the anterior substernal goiter crossed over right side of the posterior thorax.

Such glands are usually retrievable through the neck. Occasionally in large goiter, one might have to resort to a right lateral thoracotomy through the fourth or fifth intercostal space to allow adequate exposure and removal [56]. On the contrary, crossed-over substernal goiter from the anterior to the posterior mediastinal compartment or vice versa is extremely rare. It appears that because of the confined space and structures in middle mediastinal compartment, the growth of a substernal goiter occurs from the anterior left-sided goiter and crossed over the aortic arch to the opposite right side of the posterior thorax (Fig. 5.5). It may also cross over and impinge onto the brachiocephalic vein into the right posterior mediastinal compartment. The impingement on the brachiocephalic vein or on the aortic arch formed the "saddle goiter". Further downward growth into the posterior of right thorax may be mistaken for a true posterior ipsilateral substernal goiter. At this point it is important to define the trachea, as most posterior goiter will push the trachea toward the anterior. On the contrary this unique feature of anterior substernal goiter that crossed over the aortic arch to the posterior mediastinum pushes the trachea to the back. Similarly a posterior mediastinal goiter, either an ipsilateral or an contralateral goiter, may continue to enlarge extending to the anterior mediastinum particularly on the right side. The surgical implication of anterior goiters crossed over to posterior or vice versa may be important as it changes the scenario from a simple attempt of removal through a cervical approach to often a sternal split rather than a thoracotomy. It would be hazardous to attempt the removal through a cervical approach without understanding the various compartments involved and the direction of the growth. Secondary posterior substernal goiters, either an ipsilateral or a contralateral extension, may be removed through a cervical approach (Fig. 5.4) except very large goiter with incomplete removal in previous surgery would require the right posterolateral thoracotomy (Figs. 5.4 and 5.5). Special attention and care must be taken in those patients whose airway is severely compromised. It may be necessary to resort to tracheal intubation while patient is awake under topical anesthesia in order to avoid airway difficulties during induction. Tracheal intubation ensures the continuity of breathing during the surgical procedure, as traction and dissection may exert pressure against the narrowed airway. It is clear this is associated with high incidence of significant postoperative sore throat and laryngeal edema especially those with large goiter and with severe compression [57].

Operative Techniques

Anterior Substernal Goiter

Primary (isolated) anterior substernal goiters are rare clinical entities and arise primarily from the ectopic intrathoracic thyroid tissue. However, more often then not they are in fact residual portion of a goiter in the thyro-thymic remnant, which was incompletely removed in previous surgery. A sternal split is perhaps all that is required to achieve a complete removal of an isolated anterior mediastinal goiter which lies entirely within the thorax. One should not attempt to remove the goiter from cervical approach as most primary substernal goiters derive their blood supply directly from nonanatomic vessels in the anterior mediastinum. On the contrary almost all secondary anterior substernal goiters can be removed through a cervical approach without much difficulty [58]. The cervical approach allows excellent exposure and proximal control of the blood supply to the substernal goiters. After raising the superior and inferior cervical flaps it is important to divide the straps muscle on both sides to enhance the anterior exposure. To facilitate the surgery it is a good practice to start from the opposite thyroid gland with least substernal extension to provide more space in the neck. The next crucial step is to divide the middle thyroid veins and expose the lateral and the posterior prevertebral space. This is an avascular space, which provides access for safe dissection away from the carotid sheath and a cleavage point to separate the goiter from the thyroid bed. It is equally important to have a Ryle's tube inserted to allow identification of the distorted esophagus.

The identification and preservation of the external laryngeal nerve can be performed by exposure of the cricothyroid space. The priority at this point is to control the blood supply by tying the superior thyroid vessels individually. The thyroid gland can be gently dislocated to identify the Zuckerkandl tubercle and permit

the identification of the recurrent laryngeal nerve and preservation of the parathyroid glands. Once the nerve is encountered the entire cervical course can be exposed and de-roofed from the Zuckerkandl tubercle downward. Proye described the "toboggan technique" used to expose the recurrent laryngeal nerve along its course before any attempt of dissection and mobilization of the substernal goiter [59]. Although stretching of the recurrent laryngeal nerve as a cause of vocal cord paralysis is rare, it is commonly associated with large substernal goiters [60]. Thus with the nerve in sight and protected, the fascial attachments and capsular plane of the thyroid are freed with the finger above the nerve reaching downward and sweeping it toward the anterior surface. This will release the negative pressure while applying gentle upward traction to the thyroid with the other hand. The thoracic inlet is the most narrowed portion, and it is important to be in the right plane and avoid any resistance which may cause torrential bleeding on the gland especially between the gland and the posterior aspect of the manubrium and sternum. Successful delivery of the secondary anterior substernal goiter almost invariably can be achieved. Even a large goiter can be pulled out and removed without resorting to splitting of the sternum. Nonetheless if difficulty is encountered despite careful dissection, additional maneuvers should be considered. The surgeon's finger should be used to sweep around the lower end of the goiter again with simultaneous continuous traction, to confirm that all palpable adhesions have been divided [61]. A goiter extending down to the level of the aortic arch or even further sometimes may not be fully accessible with the tip of the finger. A sterile soup spoon can be used to reach further than the finger, and it may be slipped down alongside the anterolateral aspect of the thyroid, further breaking the negative intrathoracic pressure and in most instances leading to an immediate and satisfying delivery of the gland [62]. However one must be careful when using the spoon technique of the loss of tactile sensation and dexterity when reaching for the lower end of the goiter. Not infrequently Lahey's morcellation technique may be used to release the pressure in the thoracic inlet by breaching the capsule of the goiter and scooping out the content to draw the goiter out of the thorax [63]. This technique however may result in torrential venous bleeding and tumor spillage in unsuspected malignancy [56]. Failing this the collar incision can be extended by splitting the sternum with a partial sternotomy or full sternotomy to give a wider exposure of the thoracic inlet, but this is often not necessary. A sternal split should only be considered in large substernal goiter with mediastinal fixation associated with severe venous obstruction and suspected of malignancy. In addition crossed-over anterior substernal goiter either to the opposite side (Fig. 5.3) or to the posterior compartment (Fig. 5.5) and those with isthmus below the level of the manubrial notch should be best approached through a combined cervical and sternal split. This approach will allow direct visualization of the blunt finger dissection along the tissue plane toward the other compartment and avoid vital structures particularly the major vessels such as the brachiocephalic vein, superior vena cava, and the aortic arch.

Posterior Mediastinal Goiter

Posterior mediastinal goiter exclusively occurs in the right side since the brachiocephalic vein and aortic arch prevent the goiter from descending on the left. Most patients are asymptomatic but when symptomatic they are usually related to direct tracheal or esophageal compression and stretching of recurrent laryngeal nerve. Primary isolated posterior mediastinal goiter is extremely rare and in such circumstances is often necessary to have a preoperative thyroid scan to confirm the truly isolated goiter and exclude other mediastinal mass. This is important to allow adequate anatomical and functional assessment to decide on the best possible approach.

To achieve complete removal of a true primary isolated posterior mediastinal goiter, it is best approached through a primary thoracic incision either through a posterolateral or antero-lateral incision. This is because the posterior goiter may have an aberrant blood supply directly from the mediastinal. Furthermore this approach is crucial to allow visualization of the parietal pleural and protects the vital structures such as the superior vena cava and azygos vein especially toward the posterior medial region of the right thorax. On the other hand secondary posterior mediastinal goiter should be first approached through the cervical incision. As with the anterior substernal goiter a substantial portion of the blood supply comes from the inferior thyroid vessels and

hence, it is imperative to control the proximal blood vessels before exploring the mediastinal goiter. One should be careful not to attempt removal through the thoracotomy alone except only for the primary isolated posterior mediastinal goiter.

Fortunately likewise with anterior substernal goiter most secondary posterior mediastinal goiter, either an ipsilateral descend or a crossed-over goiter, can be easily removed through the cervical incision [64, 65]. The crucial step in surgery is to expose the prevertebral avascular space to facilitate optimal extraction of the goiter out of the thoracic inlet. The extracapsular blunt digital dissection of the mediastinal goiter from the surrounding structures can be performed safely from behind along this prevertebral space.

As described earlier with the course of recurrent laryngeal nerve in sight, the gentle blunt finger dissection releases the attachment and removes the extra-capsular pressure off the surrounding structure. At the same time continuous traction is applied with the other hand coupled with slow tugging from side to side to facilitate the removal of goiter out of the thorax. One must be extremely careful not to use any force or aggressive traction in the presence of fixation. If all these measures fail to extract the goiter, Lahey's morcellation technique should be considered (Fig. 5.4B). This internal scooping of the goiter content not only provides additional space but deflates the goiter further and removes the negative pressure of the surrounding structures to allow easy extraction out of the thorax [63]. A combined approach with initial cervical incision and thoracotomy is desirable when dealing with a fixed and adherent posterior mediastinal goiter, especially in reoperative recurrence goiter, large posterior goiter, goiter with deep extension below the aortic arch, and malignancy [64]. Occasionally sternal split has been used to remove the posterior mediastinal goiter. However this is not the ideal approach as sternal split will only widen the thoracic inlet but the lower end of the goiter in the posterior mediastinal is still far from accessible. The worst unaccepted scenario is to have all three approaches of cervical, sternal split, and thoracotomy in an attempt to remove the secondary posterior mediastinal goiter. Before closure the substernal space is routinely filled with saline and the lungs hyperinflated to check for any pleural leak. A suction catheter is routinely left in place for drainage of the large dead space and mandatory to insert chest drain in the respective side when there is a pneumothorax.

The presence of substernal goiter is an indication for removal in view of the potential risk of airway compression and high incidence of malignancy. In the majority of cases substernal goiters can be removed through a standard cervical incision. However a sternal split is inevitable especially in those patients diagnosed with primary isolated intrathoracic goiter and recurrent anterior substernal goiter. On the other hand thoracotomy is indicated for primary isolated posterior mediastinal goiter. However for large or recurrence posterior ipsilateral and contralateral mediastinal goiter the best surgical approach is through a combined cervical and right posterolateral thoracotomy.

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6

Thyrotoxicosis and Thyroiditis: Causes, Investigation, and Management

Johnathan G.H. Hubbard and Paul V. Carroll

Introduction

Thyrotoxicosis represents the clinical syndrome that results from exposure to elevated levels of circulating thyroid hormones. Hyperthyroidism is used to describe thyrotoxicosis resulting from overproduction of thyroid hormones by thyrocytes, with Graves' disease the commonest cause. Less frequently thyrotoxicosis occurs in the absence of hyperthyroidism, for example, a short-term thyrotoxicosis can occur when stored hormones are released in a destructive thyroiditis. The causes of thyrotoxicosis are listed in Table 6.1. Graves' disease, toxic multinodular goiter, and solitary toxic nodule account for 95% of cases and are commonly encountered in surgical practice. Causes such as Hashimoto's thyroiditis or drug-related thyrotoxicosis are uncommon but may require surgical evaluation.

Clinical Presentation and Systemic Manifestation of Thyrotoxicosis

The clinical features of thyrotoxicosis depend on the severity and duration of the disease, the age of the patient, extrathyroidal manifestations, and the specific cause of the thyrotoxicosis. Thyroid hormone excess affects almost all organ systems, and the symptoms and signs of thyrotoxicosis are similar regardless of etiology. Widespread effects occur due to the stimulation of metabolic processes and sensitization of the sympathetic nervous system (Table 6.2). In the elderly the symptoms may be more subtle than in younger patients. Apathetic thyrotoxicosis [1] occurs in elderly patients when features of sympathetic reactivity are absent, and patients may present with severe depression, weight loss, occult atrial rhythm disturbance, and a small goiter. Graves' disease has additional features, due to the immunological nature of the condition, in particular thyroid eye disease (Table 6.2).

Eye Manifestations of Thyrotoxicosis

Retraction of the upper eye lid resulting in a bright-eyed stare is common in all forms of thyrotoxicosis and is related to sympathetic overactivity. Similarly lid lag (when the upper lids move more slowly than the globe) is a general finding in the thyrotoxic individual. It is important to distinguish these features from the specific ocular manifestations of infiltrative ophthalmopathy that is characteristic of Graves' disease.

Thyroid Gland

Both Graves' disease and toxic nodular goiter are usually associated with enlargement of the thyroid gland. Toxic adenoma and multinodular goiter commonly result in an asymmetric gland. The goiter of Graves' disease is typically

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Table 6.1. Cause of thyrotoxicosis

Group	Disease	Relative frequency
Thyrotoxicosis of thyroidal origin	Graves' disease	70%
	Toxic adenoma	5%
	Multinodular toxic goiter	20%
	Iodine-induced thyrotoxicosis	<1%
	TSH-secreting adenomas	<1%
	Neonatal thyrotoxicosis	<1%
Associated with thyroid destruction	Subacute thyroiditis	3%
	Silent thyroiditis	3%
	Amiodarone-induced thyrotoxicosis (type 2)	<1%
Thyrotoxicosis of nonthyroidal origin	Factitious thyrotoxicosis	Very rare
	Thyroid hormone poisoning	Very rare
	Struma ovarii	Very rare
	Metastatic thyroid cancer	Very rare

Table 6.2. Systemic effects of thyrotoxicosis

System	Effects
General	Weight reduction, nervousness, irritability, heat intolerance, fatigue, poor sleep
Skin	Warm, moist palms, hyperhidrosis, urticaria, itching, exacerbation of eczema
	*Dermopathy: violaceous, nonpitting induration of pretibial skin (pretibial myxoedema)
	*Acropachy: clubbing
Eye	Lid lag and retraction
	*Periorbital edema, chemosis, exophthalmos, ophthalmoplegia, redness, loss of vision
CNS	Irritability, worsening of psychiatric conditions, stupor, coma
CVS	Tachycardia, cardiomegaly, heart failure, rhythm disturbance
Respiratory	Dyspnoea
Bone	Reduced bone mineral density
Fertility/reproduction	Gynecomastia, infertility, light or absent menstrual periods
Metabolic	Hyperglycemia, hypercalcemia
Gastrointestinal	Diarrhoea/hyperdefecation
Neuromuscular	Tremor, myopathy, paralysis

*Features specific to Graves'.

visible, diffusely enlarged, smooth, and may be associated with a bruit or thrill.

Laboratory Diagnosis of Thyrotoxicosis

The biochemical diagnosis of thyrotoxicosis is confirmed on blood tests demonstrating elevated levels of circulating thyroid hormone levels with associated suppression of thyroid-stimulating hormone (TSH). Thyroxine (T4) and triiodothyronine (T3) are most commonly measured in their respective free states (free T4 and free T3 [2]). TSH is suppressed in the vast majority of thyrotoxic individuals due to negative feedback of thyroid hormones on the anterior pituitary, but can be normal or elevated when a TSH-secreting pituitary tumor is present or with thyroid hormone resistance [3]. Subclinical thyrotoxicosis exists when TSH is suppressed without overt

elevation of free T4/T3 [4]. Once the diagnosis of thyrotoxicosis is confirmed the cause should be established. The presence of extra-thyroidal signs and the size and shape of a goiter are informative as to the likely cause, although in 30% a goiter may not be palpable [3].

Antithyroid Antibody

Detection of TSH-receptor antibodies (TRAb) in the blood of the thyrotoxic patient is useful in confirming Graves' disease as the cause. Most laboratories use in vitro methodology that assesses TSH-binding-inhibiting immunoglobulins (TBII). Positive TBII tests are found in approximately 90% percent of patients with Graves' disease with 99% specificity. TBII is usually used when the clinical picture is unclear or in cases of pregnancy to guide on the risk of neonatal thyrotoxicosis. Antithyroid peroxidase and antithyroglobulin antibodies are commonly measured in the thyrotoxic patient to determine underlying autoimmune thyroid disease. They can be found in up to 90% of patients with Graves' disease but may be present in patients with thyroiditis.

Nuclear Medicine Imaging (Thyroid Scintigraphy)

The pattern of uptake on a nuclear medicine scan (radioiodine or technetium-99m) can be useful in establishing the cause but is not necessary in all cases of thyrotoxicosis (Table 6.3). Any patient with a dominant nodule should be considered for thyroid fine needle aspiration cytology (FNA) to exclude malignancy. However, the cytological interpretation of FNAs taken from toxic nodules is problematic due to their hyperplastic nature. This causes an increased yield of atypical cells (Thy3), making it difficult to exclude malignancy, despite the fact that most nodules are benign. Therefore care should be taken in the selection of such patients for FNA.

Table 6.3. Diagnosis and pattern of radioiodine uptake in thyrotoxicosis (with suppressed TSH)

Low uptake
Silent/postpartum thyroiditis
• Nontender thyroid, + antithyroid antibodies
subacute/de Quervain
• Recent URT viral infection, tender thyroid, fever, High ESR
Struma ovari
• Abdominal uptake
Iodine induced (e.g., IV radiological contrast, amioderone)
• Usually on background of MNG
Thyrotoxicosis factitia
High uptake
Graves' disease
• Diffuse uptake
Toxic MNG
• Nodular/patchy uptake
Toxic Nodule
• Uptake in nodule with suppressed normal thyroid
Trophoblastic tumor
• Raised β HCG
Lymphocytic thyroiditis
• Positive thyroid autoantibodies

Graves' Disease

Exophthalmic goiter is the most common cause of thyrotoxicosis, accounting for approximately 70% of cases. It was first described in 1786 by Parry, an English physician from Bath, but he did not publish his findings during his lifetime. In the English-speaking world it has become known as Graves' disease after Robert Graves, an Irish physician who described it in the early nineteenth century, while in mainland Europe it is known as Basedow's disease following von Basedow's description in Germany in 1840.

Graves affects 2% of women, with a female to male ratio of 10:1 [5, 6]. It is an autoimmune disease that can occur at any age, although it typically affects young women between 20 and 40 years of age. Geographical variations are reported, with peak incidence occurring in older patients in Iceland and Sweden [7]. Graves' disease is more common in tobacco users [8].

Pathogenesis

Genetic factors are thought to be important in the development of Graves' disease. Studies in monozygotic twins have shown higher concordance

rates (30–50%) compared with dizygotic twins (5%) suggesting a genetic component is involved [9], although environmental factors have an important role. Graves' disease is more common in Caucasians and has been liked to certain major histocompatibility complex-human leukocyte antigens (MHC-HLA) class II gene polymorphisms, most notably, DRB3 [9, 10]. Polymorphisms of the *CTLA-4* gene (cytotoxic T-lymphocyte-associated-4) are more common in individuals with Graves' disease. CTLA-4 is a T-cell-surface molecule important in T-cell activation, alongside HLA class II antigen presentation [10]. Polymorphisms to such genes may have a role in susceptibility to both autoimmune and infectious diseases. Other autoimmune conditions are associated with Graves' disease and these are listed in Table 6.3. Debated triggers for Graves' disease include stress [11], smoking [7], and antibodies to infections including Yersinia enterocolitica [12, 13] which may cross-react with TSH receptors.

The pathogenesis of Graves' disease has not been fully elucidated. Key in the process are antibodies acting against the TSH receptor (TSH-stimulating antibodies are found in the sera of >90% of untreated cases [3]). Patients with Graves' have been found to have three classes of antibodies (neutral, blocking, and stimulatory) [14]. The clinical picture depends on the balance of these antibodies [15]. In classical Graves' hyperthyroidism the preponderance of stimulatory antibodies results in the overproduction of thyroid hormone in an unregulated fashion. Antibodies to other thyroid antigens are frequently present (antithyroperoxidase and antithyroglobulin). Inflammatory cells infiltrate the thyroid with the production of cytokines. There is associated hyperplasia and hypertrophy of thyroid follicles resulting in goiter formation. The combination of both stimulatory and destructive thyroid antibodies may explain the variable course of Graves following medical treatment, with remissions and hypothyroidism in some patients.

Diagnosis

The diagnosis of Graves is confirmed clinically when thyrotoxicosis is present in a patient with a diffuse goiter, with extra thyroidal signs such as ophthalmopathy or dermopathy. Antithyroglobulin and antithyroid peroxidase antibodies are elevated in 80%. Thyroid-stimulating antibodies are measured in cases where the diagnosis is uncertain. Thyroid scintigraphy shows diffuse uptake in the thyroid and can be used to distinguish Graves from other causes of thyrotoxicosis (e.g., toxic multinodular goiter and a solitary toxic nodule).

Thyroid Eye Disease (Thyroid Ophthalmopathy, Graves' Ophthalmopathy)

Eyelid retraction and lag are common nonspecific eye signs which can occur in all causes of thyrotoxicosis. They are caused by the sympathetic innervation of levator palpebrae superioris carried via the third cranial nerve. Specific Graves' ophthalmopathy is clinically evident in 30% of patients [3]. Eye signs include eye discomfort and grittiness, proptosis (30%), and extraocular muscle involvement (10%), while corneal involvement and optic nerve compression are uncommon.

The cause of ophthalmopathy remains under investigation but is thought to be due to an immune response to antigens present in retroorbital tissues that are shared with the thyroid, or antigens which can cross-react with the TSH receptor. Orbital adipocytes and fibroblasts have been shown to express TSH receptors [16, 17]. The results are edema, glycosaminoglycan deposition, and fibrosis of retroorbital tissue and extraocular muscles. Ophthalmopathy is more common in smokers [18, 19], and rarely the signs can be unilateral (10%). CT and MRI of the orbit are useful in determining degree of extraocular muscle enlargement. Treatment for milder forms is directed at symptom control and includes lubricating eye drops, elevation of the head of the bed, and occasionally diuretics. Active inflammation may respond to immunosuppressive treatments including corticosteroids (used as a first-line treatment) and azathioprine (Figs. 6.1 and 6.2). External beam radiotherapy is commonly used to reduce inflammation and enlargement of extraocular muscles. In cases where the optic nerve is threatened and acuity reduced orbital decompression by an experienced surgeon may be necessary.

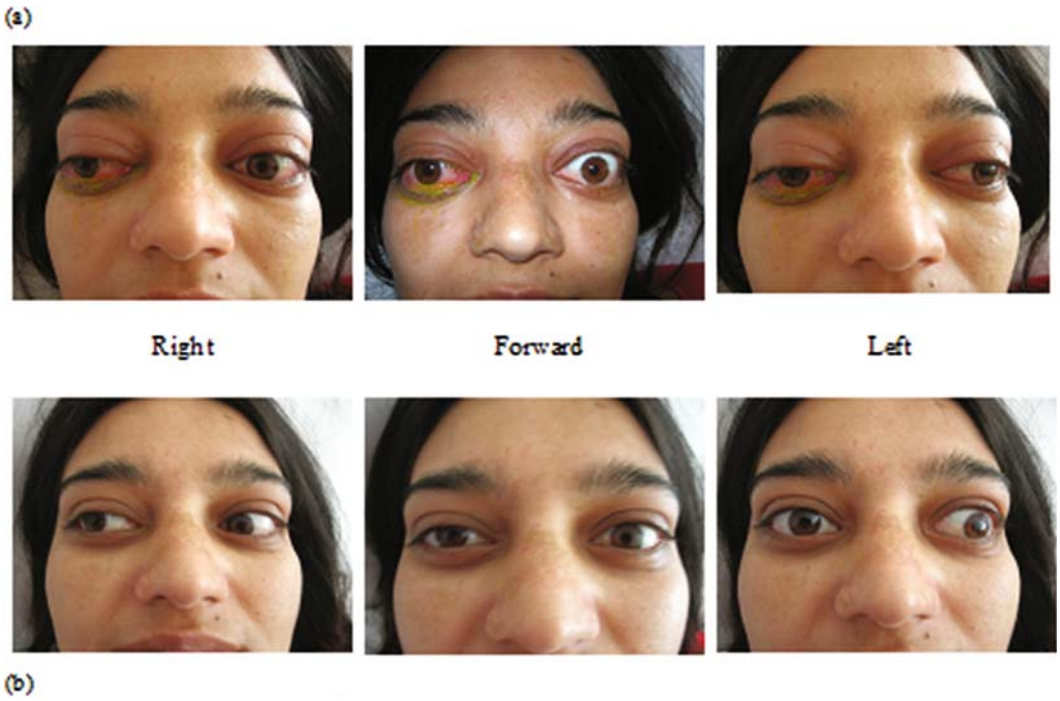

Fig. 6.1. Eye movements (**A**) pretreatment and (**B**) day 6 after initiation of treatment with methylprednisolone.

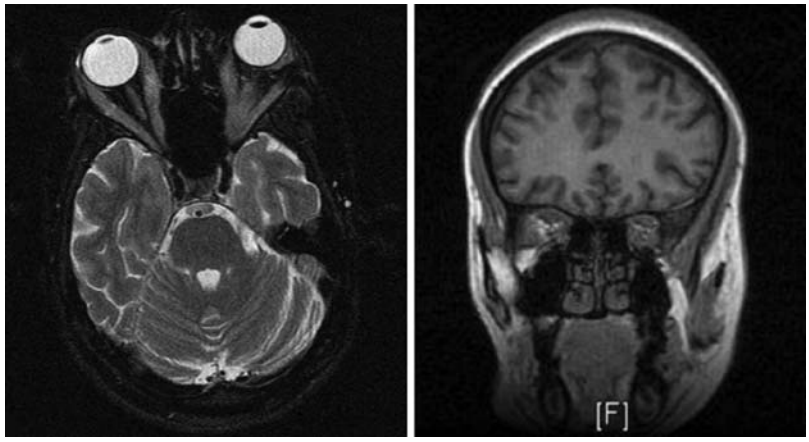

Fig. 6.2. Orbital MRI demonstrating bilateral proptosis, enlarged ocular muscles, and compressive optic neuropathy. (**A**) Axial view; (**B**) coronal view.

Identifying the Etiology of Thyrotoxicosis

Commonly the etiology is clinically evident and the treatment choice straightforward. The presence of thyroid eye disease and a diffuse goiter with a bruit are classical features of Graves' disease. Distinguishing between Graves' disease and toxic nodular disease in the middle-aged individual without extra-thyroidal manifestations may be more difficult. In addition to clinical assessment, measurement of thyroid antibodies, high-resolution ultrasonography, and nuclear medicine

imaging may be helpful. The absence of conventional antibodies does not exclude autoimmune thyroid disease. The pattern of tracer uptake on the nuclear medicine scan [iodine-123 (I-123), I-131, or technetium-99m] can be helpful in identifying toxic nodularity particularly.

Clarifying the etiology of thyrotoxicosis within 12 months postpregnancy can be particularly difficult. Destructive inflammatory thyroiditis is common during this period, but similarly Graves' disease may present or be exacerbated at this time. The absence of (or very low) isotope uptake on a nuclear medicine scan is supportive of destructive thyroiditis in such cases (and can be performed with careful planning in the breast-feeding mother).

Treatment of Thyrotoxicosis

Antithyroid Drugs

Antithyroid drugs are used to render a patient euthyroid to either induce a remission or as preparation for definitive treatment (radioiodine or surgery). The principle thioamide antithyroid medications used are Methimazole (USA/Europe) or Carbimazole (UK), and Propylthiouracil (PTU). Carbimazole is metabolized to Methimazole. These drugs are concentrated within the thyroid and interfere with the action of thyroid peroxidase with consequent reduction in thyroid hormone synthesis. In addition PTU partially inhibits the conversion of T4 to T3 in peripheral tissues, potentially reducing the levels of the active T3 hormone more quickly than carbimazole, although this is not clinically important in routine use [20]. PTU is preferred in pregnancy as it is less likely to cross the placenta due to protein binding. Propranolol can be used to block the sympathetic effects of thyroid hormones whilst antithyroid medication takes effect (2–4 weeks). Antithyroid medication is generally well tolerated and may be used in a titration regimen or as part of a "block and replace" strategy.

Treatment Strategies

In the titration regimen a high starting dose of carbimazole is gradually reduced to maintain a euthyroid state. In block and replace, a high dose (e.g., 40 mg carbimazole daily) is continued to fully block endogenous thyroid hormone production and thyroxine is added after 4–6 weeks to maintain an euthyroid state. Monitoring is required as the dose of thyroxine may need adjustment. Treatment is optimally continued for 12–18 months based on analysis of four randomized clinical trials [21]. The dose of methimazole used does not influence subsequent recurrence rates [22]. Remission is variable, but about 60% of patients develop subsequent recurrence [20, 21].

Side Effects

Side effects of the thioamide drugs can be major or minor. Major side effects are rare and include agranulocytosis in 0.5% [22, 23], hepatitis [24], aplastic anemia, and vasculitis (with PTU) [25] and require the medication to be stopped. On starting thioamide medication patients should be warned to seek urgent medical advice should they develop a sore throat, mouth ulceration, or fever. Minor side effects occur in up to 5% of patients [20] including a skin rash, pruritis, urticaria, arthralgia, myalgia, and transient leukopenia. These effects may respond to a reduction in dose or substitution of one thioamide for another, although there can be cross-reactivity.

Radioiodine Therapy

Radioiodine can be used as first-line definitive treatment, or for recurrence following treatment with antithyroid drugs or subtotal thyroidectomy (ST). Its use was first reported in the early 1940s [26], and it rapidly became the main form of definitive therapy, replacing the role of surgery for small uncomplicated goiters [27]. Today the use of radioiodine varies throughout the world with a predominate role as the primary treatment of Graves' in the USA [28, 29], while in Europe and Japan antithyroid drugs are predominantly used as first-line therapy [30, 31].

Radioiodine is most suitable for patients with a small goiter and in the absence of ophthalmopathy. It is contraindicated in pregnancy, for those breast feeding, or for those planning to become pregnant within 4–6 months of therapy. Radioiodine may be unacceptable to those with contacts with children due to the need to avoid

close contacts for several weeks following treatment. This can include parents, grandparents, and those who work with children. Radioiodine is relatively contraindicated in children due to the concerns of inducing thyroid cancer and secondary neoplasias in later life, although radioiodine is used in some pediatric centers, and studies to date have not confirmed these concerns [32]. Radioiodine is usually avoided in those with severe ophthalmopathy, as it is recognized that ophthalmopathy worsens in about 15% of patients following treatment [19]. Patients with stable eye signs can be given a supervised course of glucocorticoid starting at the time of therapy to prevent a deterioration of their ophthalmopathy.

Prior to radioiodine treatment patients should have their hyperthyroidism controlled and are typically treated with a thioamide drug until they are clinically euthyroid, although radioiodine is frequently given without pretreatment for those with mild hyperthyroidism [29]. Antithyroid drugs may be stopped several days prior to treatment to maximize radioiodine uptake and prevent treatment failures. Noncontrolled studies suggest PTU has a longer radioprotective effect than carbimazole [33], although no difference was found between the two classes of drugs in a recent meta-analysis [34]. Radioiodine is administered orally as I-131, which emits β particles that are destructive to thyroid follicular cells. The effects of radioiodine are not immediate and continue for months following treatment. Symptomatic improvement takes approximately 6–8 weeks. Hypothyroidism is the major consequence of radioiodine treatment occurring in approximately 20% of patients at one year, and eventually causes permanent hypothyroidism in almost all patients [3]. Thyroid replacement therapy is commenced when TSH levels start to rise above the normal range. For patients with persistent hyperthyroidism following an initial radioiodine therapy a second dose can be administered at 4–6 months [29, 35].

Surgical Treatment

Surgery is the treatment of choice for patients with large goiters, with compressive symptoms, when radioiodine is contraindicated, with an FNA suspicious for malignancy, with severe ophthalmopathy, for children, or for patient preference. Surgery provides tissue for histological assessment not provided by radioiodine therapy. Incidental malignancy is reported in around 5% of cases, although the incidence of malignancy may be higher in patients with discrete nodules and Graves (21% [36]).

Preparation for Surgery

Prior to surgery hyperthyroidism should be controlled, to reduce the risk of thyroid storm in the postoperative period. Lugol's iodine (3 drops tds) can be administered 7–10 days prior to surgery to reduce the vascularity of the thyroid [37] as an adjunct to antithyroid medications to aid the surgeon, although this is not necessary for all patients. For patients with difficulty to control thyrotoxicosis and those intolerant of thioamide drugs, a team approach with endocrinologists and anesthetists is particularly important. High dependency care may be necessary for this select group of patients. Large doses of iodine can be given prior to surgery to stun the thyroid (Wolf Chaikoff effect). This can be achieved using large doses of Lugol's iodine or iodine-containing radiological contrast agents, such as sodium ipodate [38]. B blockers should be used to control the adrenergic effects provided there are no relative contraindications such as asthma when a cardioselective B blocker may be considered.

Subtotal Thyroidectomy

Historically, ST has been the surgical procedure of choice in Graves' disease [39]. A meta-analysis of 35 studies from 1965 to1998 demonstrated that 93% of 7,241 patients underwent a ST compared with 538 undergoing total thyroidectomy (TT) [40]. The theoretical advantages and disadvantages of the procedures are shown in Table 6.4.

Thyroid Remnant Size

The procedure of ST has not been well defined, which makes assessing outcomes of surgery problematic. Residual thyroid remnant size has varied between 2 and 12 g [40] although is

Table 6.4. Theoretical advantages and disadvantages of subtotal total thyroidectomy

Subtotal thyroidectomy
Advantages
Reduced complications
Hypoparathyroid
RLN
Postoperative avoid thyroxine
Disadvantages
Risk hypothyroidism
Short and longer term
Risk persistent/recurrent hyperthyroidism
Thyroid tissue remains in unexpected malignancy
Long-term follow-up required
Total thyroidectomy
Advantages
Certain outcome
Permanent hypothyroidism
Malignancy adequately treated
Complications not increased in experienced hands
Disadvantages
Thyroxine to all

generally <4 g in recently treated patients. The estimation of remnant size can be imprecise and various methods have been used to assess this, including surgeons eye [40, 41], measuring volume [42], and weighing pieces of resected thyroid to compare with the remnant in situ [43, 44]. The thyroid remnant has also been adapted to goiter size, leaving a remnant of approximately 10% estimated goiter weight [45]. ST can be performed as a bilateral subtotal resection or unilateral lobectomy with remnant on the contralateral side.

Surgical Objectives

The primary aim of definitive treatment is to resolve hyperthyroidism and avoid recurrence. This objective is not achieved in all patients undergoing ST. Remnant size is related to rates of persistent/recurrent hyperthyroidism and consequently remnant sizes have become smaller to reduce this risk. Reported postsurgical hyperthyroidism rates have varied from ~25%, with remnants >6 g, to ~9%, with remnants <4 g [42, 44]. Overall 7.9% of 6703 ST patients developed recurrence of hyperthyroidism with an average reported remnant weight of 6.1 g [40].

A further aim of ST is to leave the patient euthyroid without the need for thyroxine. Around 25% develop hypothyroidism. Remnant size is negatively correlated to hypothyroidism with an 8.9% reduction in hypothyroidism rates for each residual gram of thyroid remnant [40]. While most cases of hypothyroidism occur within 12–18 months of surgery, hypothyroidism can develop at a later stage [46].

Total Thyroidectomy

TT has been increasingly proposed as the surgical procedure of choice in Graves' disease [43, 47, 48], because ST does not achieve its two main aims in 30–40%. Following TT patients have a certainty about their thyroid status (unlike ST), and incidental malignancy which is found in ~5% is appropriately treated (9% in some single center series) [40]. The published data suggest that there is no significant difference in complication rates (RLN injury and hypoparathyroidism) between ST and TT in experienced hands [40, 43].

Surgery has a beneficial effect of reducing TSH receptor antibody levels for many patients, which appears to be similar for both surgical procedures at 12 months, but may be better maintained beyond 12 months in TT patients [49]. While surgery is preferred to radioiodine in patients with ophthalmopathy, the course of eye disease for an individual patient following surgery remains unpredictable.

Thyroid Storm

This rare but potentially life-threatening situation is an acute exacerbation of thyrotoxicosis with marked hypermetabolism and adrenergic response. It can be precipitated by definitive thyroid treatment (surgery or radioiodine) in a patient with inadequately controlled thyrotoxicosis or in a patient with thyrotoxicosis following

parturition or during a severe illness, e.g., uncontrolled diabetes, severe infection, or myocardial infarction. Hyperpyrexia is the striking feature but tachycardia, AF, heart failure, agitation, confusion, vomiting, diarrhoea, coma, and shock can occur. Patients are best managed in an intensive care environment. Treatment is aimed at (1) reducing thyroid hormone secretion, e.g., PTU, Lugol's iodine; (2) supportive therapy, e.g., propranolol, steroids, external cooling, IV fluids; and (3) treating any underlying cause. Ensuring adequate preparation of surgical patients preoperatively should prevent this situation.

Toxic Multinodular Goiter and Toxic Adenoma (Plummer's Disease)

A long-standing multinodular goiter can develop autonomous nodules leading to thyrotoxicosis. It is the most common cause of thyrotoxicosis in the elderly (>60 years). The risk increases with age and iodine intake, and presentation can occasionally be precipitated, following the administration of iodine-containing radiological contrast media (Jod–Basedow effect). A suppressed TSH with normal free T3 and T4 in the context of a long-standing goiter should arouse suspicion of developing autonomy. Thyroid scintigraphy shows patchy diffuse uptake with hot and cold areas.

A solitary toxic nodule is the cause of ~5% of thyrotoxicosis. The biochemical diagnosis is confirmed as in other causes. Thyroid scintigraphy confirms the presence of a hot nodule with suppressed uptake in the remainder of the thyroid.

Medical control of thyrotoxicosis does not induce remission of toxic nodules as in the case of Graves' disease. Definitive treatment can be radioiodine for a noncompressive and cosmetically acceptable goiter, a small toxic nodule, and for those wishing to avoid surgery. In those with a toxic nodule the risk of radioiodine-induced hypothyroidism is small due to the toxic nodule suppressing and inhibiting radioiodine uptake on the remaining thyroid. The effects of radioiodine are delayed and it usually fails to resolve the goiter [50].

Patients should have the hyperthyroidism controlled preoperatively as in Graves', although Lugol's iodine is not helpful in the preoperative preparation and can make hyperthyroidism worse.

TT is the surgical procedure of choice for a large toxic multinodular goiter. This avoids possible regrowth of the goiter and recurrent thyrotoxicosis. Thyroid lobectomy is the surgical procedure of choice for a solitary toxic nodule as it provides tissue for histology, while the normal contralateral lobe means the patient is likely to be euthyroid postoperatively.

Amiodarone and Thyrotoxicosis

Amiodarone is a widely used antiarrhythmic drug that contains two atoms of iodine per molecule. It is recognized to induce thyrotoxicosis, which can occur after years of treatment, through two possible mechanisms: iodine-induced thyrotoxicity and amiodarone-induced thyroiditis. The standard maintenance dose of amiodarone for the cardiac patient (200 mg/d) can increase serum iodide levels by 40-fold. This excess may exacerbate thyrotoxicosis in prone individuals with underlying thyroid disease and is referred to as an amiodarone-induced thyrotoxicosis (AIT-type I). As a result of cytotoxic effects amiodarone and its metabolites may have destructive effects on thyrocytes resulting in AIT-type II. Distinguishing between these types of AIT can be difficult. In AIT-type II thyroid uptake of isotope is absent or markedly reduced. The very long half-life of amiodarone results in long-term effects on the thyroid, even months after cessation of amiodarone. High-dose thioamide drugs and potassium perchlorate can be used to treat AIT-type I, but commonly thyroidectomy is required, especially if continuation of amiodarone treatment is indicated. Glucocorticoids are used to reduce destructive thyroiditis and are effective in controlling thyrotoxicosis in many patients with AIT-type II but often the duration of treatment is 6 months or more and thyroidectomy should be considered in individual cases.

Thyroiditis

This term describes a group of disorders that result in inflammation of the thyroid gland. The etiologies and pathogenesis of conditions causing thyroiditis vary considerably and the causes are listed in Table 6.5.

Table 6.5. Classification of thyroiditis

Infectious thyroiditis
Bacterial, fungal, parasitic
Subacute (De Quervain) thyroiditis
Autoimmune thyroiditis
Hashimoto thyroiditis
Lymphocytic thyroiditis
Postpartum thyroiditis
Thyroiditis associated with other thyroid disorders
Graves' disease
Focal thyroiditis in papillary carcinoma
Radiation thyroiditis
Miscellaneous
Sarcoidosis, drug-associated, amyloidosis

Infective thyroiditis (excluding viruses) is rare and usually due to suppurative bacterial infections. Gram-positive organisms, streptococcal, and staphylococcal species are the most common agents, and spread to the thyroid is usually blood-borne. Pain, tenderness, and increased temperature are the characteristic findings. Ultrasound examination can be useful and guide FNA for diagnosis. Appropriate antibiotic therapy is curative in the majority, but lobectomy may be required, especially in recurrent disease.

Subacute thyroiditis is a well-defined, self-limiting entity that results in painful thyroid inflammation with release of thyroid hormones. *There is a female preponderance and viral infection is considered the pathological mechanism*. The histological appearance is of granulomatous infiltration of the thyroid. Thyroid antibody levels may be detectable and rise during the acute phase of thyroiditis. There may be an underlying genetic predisposition to the condition. Treatment is directed at symptoms and pain relief. Antiinflammatory medications including corticosteroids may be used in more severe cases. Some patients develop a transient hypothyroidism during the recovery phase, and thyroidectomy is very rarely indicated.

Struma lymphomatosa (Hashimoto's thyroiditis) was first described in 1912 and refers to autoimmune thyroiditis with associated lymphocytic infiltration of the thyroid. The precise nature and etiology of autoimmune thyroiditis have not been fully elucidated. Genetic factors are certainly important and defects in antigen-presenting processes are considered central in the pathogenesis. Thyroid antibodies (especially peroxidase and thyroglobulin) are usually demonstrable in patients with Hashimoto's thyroiditis. The clinical presentation is variable but may include a firm rubbery goiter with pressure symptoms and discomfort in the neck, thyroiditis with thyrotoxicosis (hashitoxicosis), or hypothyroidism. Thyroxine supplementation is necessary in all hypothyroid individuals. Antiinflammatory medication is generally not needed, and similarly surgery has no major role in the treatment of autoimmune thyroiditis.

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7

Molecular Biology of Thyroid Cancer

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Introduction

There have been significant advances in our understanding of the molecular biology of thyroid cancer, and many of these studies have important clinical ramifications or applications to optimizing patient management. For example, the discovery of the germline mutation in the RET proto-oncogene that is responsible for hereditary medullary thyroid cancer has resulted in the ability to perform prophylactic thyroidectomy in at-risk individuals and more effective screening of at-risk family members, and the realization that genotype–phenotype associations are present. Genetic studies also provide a more precise estimate of tumor aggressiveness and identify individuals predisposed to having additional endocrine tumors (hyperparathyroidism and pheochromocytoma).

Thyroid cancer is an ideal model for studying the genetic changes involved in the development and biological behavior of cancer because of its varying clinical behavior, from the usually benign-acting occult papillary thyroid carcinoma (PTC) to the almost uniformly lethal anaplastic thyroid carcinoma (ATC). There is a growing body of literature on the molecular biology of thyroid cancer which has improved our understanding of thyroid carcinogenesis. This chapter will focus on the key genetic and epigenetic changes that are present in most thyroid cancers of follicular cell and parafollicular cell origin, and the genetic and clinicopathologic associations that have emerged from many of these studies.

Common Genetic Changes Found in Thyroid Cancer

Several genetic changes contribute to thyroid carcinogenesis (Table 7.1). The functions of these genetic alterations are diverse and involve biological processes such as cell-surface tyrosine kinase receptors, cytoplasmic signaling proteins, and nuclear transcription factors. These genetic changes are closely related to thyroid tumor development and behavior and a working model of genes involved in thyroid carcinogenesis has been proposed (Fig. 7.1). Some of these genetic changes have unique biological features which can be used for various clinical applications such as improving diagnostic accuracy, predicting disease aggressiveness, and as targets for therapy.

Medullary Thyroid Cancer

RET

The *RET* (rearranged during transfection) gene is located on chromosome 10q11.2, and encodes a transmembrane tyrosine kinase. The RET tyrosine kinase receptor has three domains. The

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Table 7.1. Mutations found frequently in thyroid tumors

Genes	Prevalence	Main function	Phenotypical characteristics
RET[§]	100%	Receptor tyrosine kinase	Familial MTC, MEN 2
Ras	20–50%	Intracellular signaling	FA, FTC, follicular variant PTC
BRAF	30–80%	Intracellular signaling	Classical PTC, tall cell variant PTC
RET/PTC rearrangement	5–35% 55–85%*	Receptor tyrosine kinase	PTC, radiation-induced PTC
NTRK rearrangement	5–10%	Receptor tyrosine kinase	PTC
PAX8/PPARγ	26–63%	Transcription factor	FTC
P53	22–83%	Tumor suppressor gene	Anaplastic thyroid carcinoma
PTEN	6–8%[¶]	Tumor suppressor gene	Cowden's disease, FTC, ATC, PTC

Abbreviations: FTC = follicular thyroid carcinoma, PTC = papillary thyroid carcinoma, MTC = medullary thyroid carcinoma, MEN = multiple endocrine neoplasia, FA = follicular adenoma.
* = prevalence in radiation-induced PTC. ¶ = prevalence in sporadic tumor. In Cowden's disease, germ-line mutation present in about 80% of the patients. § = germ-line mutation.

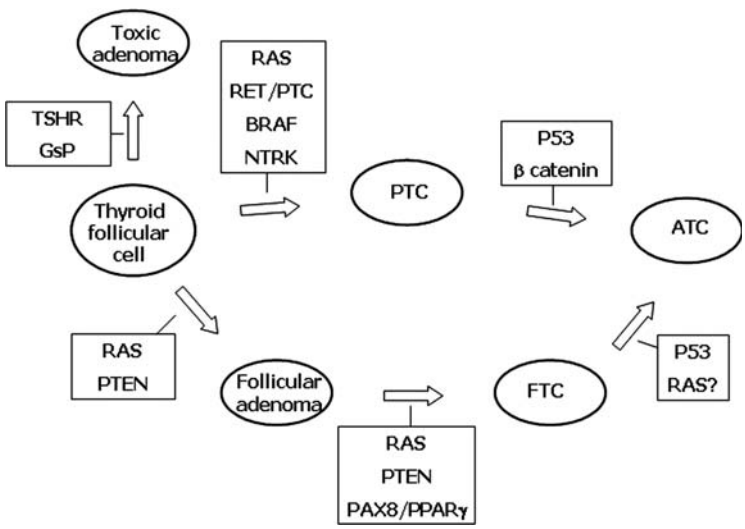

Fig. 7.1. Common genetic changes in thyroid tumors and their contribution to tumorigenesis.

extracellular domain (ECD) has cadherin-like and cysteine-rich regions [1]. There is also a transmembrane domain (TMD), as well as an intracellular tyrosine kinase domain (TKD) with two kinase regions, which are responsible for activating the mitogen signaling cascade.

RET is usually expressed in cells of neural crest origin and in the urogenital tract. Glial cell-derived neurotrophic factor (GDNF) is the main ligand for RET; however, other ligands such as neurotrophic growth factor can activate RET through interreceptor signal transduction [2]. After ligand binding to RET, homodimerization of the receptor occurs, which activates mitogen signaling. Ligand binding also results in autophosphorylation of the docking sites in the intracellular TKD receptors, which induce cellular proliferation, differentiation, increased motility, and calcium release [3].

Multiple endocrine neoplasia (MEN) 2A was linked to chromosome 10q11 in 1987, and the responsible germline point mutation in the RET

protooncogene in FMTC and MEN 2A was identified in 1993 [4]. Numerous germline activating point mutations in the RET protooncogene have been identified and are responsible for hereditary medullary thyroid cancer (MEN 2A, MEN 2B, and FMTC), and also occur as somatic mutations in approximately 25% of sporadic tumors (Fig. 7.2) [5]. The codon 634 mutation is most commonly found in patients with MEN 2A and FMTC (85%) [6]. Mutations in codon 609, 611, 618, 620, and 804 account for the remaining 10–15% of cases [7]. Other less common RET mutations also exist and are found more often in FMTC. The RET mutation sites in MEN 2B are restricted to codons 918 (95%) and 883 (5%) [6]. The clinical application, genotype–phenotype associations in hereditary medullar thyroid cancer are discussed in Chapter 11 and 43.

Thyroid Cancer of Follicular Cell Origin

RAS

The RAS protooncogene encodes a membrane-associated guanosine triphosphate (GTP)-binding protein. There are three forms of this gene – H-RAS, K-RAS, and N-RAS – which are located on chromosomes 11p11, 12p12.1, and 1p13.2, respectively. RAS proteins are located in the inner surface of the cell membrane and play a key role in G-protein-coupled receptor tyrosine kinase signal transduction [8]. RAS is activated after GTP binding to its docking site in codon 12/13 of exon 1, and deactivated by a GTPase which has a docking site domain in codon 61 of exon 2.

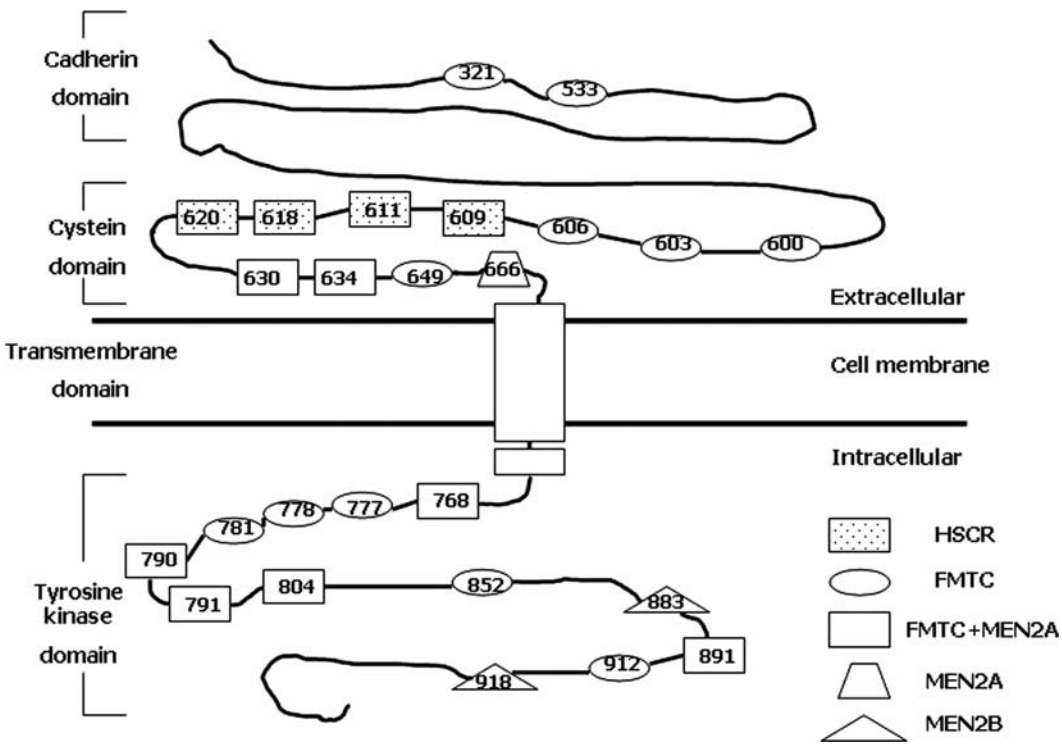

Fig. 7.2. Genotype–phenotype correlation in hereditary medullary thyroid carcinoma. Location of each mutated codon is as follows: codon 321 = exon 5, codon 533 = exon 8, codon 600–codon 620 = exon 10, codon 630–codon 666 = exon 11, codon 768–codon 791 = exon 13, codon 804 and codon 852 = exon 14, codon 883 and codon 891 = exon 15, codon 912 and codon 918 = exon 16. Square indicates mutated codon which is appeared both in FMTC and in MEN 2A. *abbreviation: HSCR = Hirschsprung's disease. MTC harboring this codon mutation may accompany with Hirschsprung's disease. MEN = multiple endocrine neoplasia syndrome. FMTC = familial medullary thyroid carcinoma.

Activated RAS binds to various downstream effector molecules such as GAP, NORE1, PKC, MEKK, PI3K, and RAF, which regulate cell proliferation and survival. Point mutations in RAS in thyroid tumors typically occur in codon 12/13 in exon 1 and codon 61 in exon 2. These mutations cause increased affinity to GTP or decreased affinity to GTPase, which in turn leads to constitutive activation of downstream effector molecules. The mitogen-activated protein kinase (MAPK) pathway via BRAF and the PI3K/Akt pathway are the main signal pathways that are activated by RAS mutation in thyroid tumors. Hou et al. [9] have suggested that RAS-PI3K/Akt activation contributes to FTC development while RAS–RAF–MAPK pathway activation selectively leads to PTC, based on their findings of more frequent PI3K/Akt-related genetic changes in FTC.

In thyroid cancer, the prevalence of RAS mutations is variable. Vasko et al. [10] performed a pooled analysis of 269 mutations in H-RAS, K-RAS, and N-RAS from 39 previous studies. The rates of mutation involving N-RAS exon 1 and K-RAS exon 2 were less than 1%. Mutations of codon 61 of N-RAS were significantly more frequent in follicular tumors (19%) than in PTC (5%) and significantly more frequent in malignant (25%) compared with benign (14%) tumors. H-RAS mutations in codons 12/13 were found in 2–3% of all types of tumors, but H-RAS mutations in codon 61 were observed in only 1.4% of tumors, and almost all of them were malignant. Both H-RAS mutations in codons 12/13 and mutations of codon 61 of N-RAS occur more frequently in follicular adenoma than in follicular thyroid carcinomas (FTC). Nikiforova et al. [11] have also reported a higher frequency of RAS mutation in follicular adenoma compared with follicular carcinoma. RAS mutations are also found in some PTCs [12].

RAS point mutations have been suggested to be an early event in the tumorigenesis of FTC because they occur in both follicular adenomas and FTC. However, considerable variability in the prevalence of RAS mutation has been reported. These variations may be due to factors such as radiation exposure, iodine intake, different pathologic classification, or technical factors [8]. Poorly differentiated and ATCs are more likely to have RAS mutations in some reports [13].

RAS mutations may also be associated with more aggressive disease and a poorer prognosis in thyroid cancer. In a recent report, transgenic mice carrying the N-RAS gene mutation developed poorly differentiated thyroid carcinomas [14]. Furthermore, RAS signaling through the downstream MAPK and PI3K/Akt pathways stimulate dedifferentiation of follicular thyroid cells [15]. Taken together, these findings suggest that RAS is involved in both the initiation and the progression of some thyroid cancers.

RET/PTC Rearrangement

Another important mechanism in the activation of the RET tyrosine kinase in follicular thyroid cells is the inter- or intrachromosomal rearrangement of RET to another gene; unlike the activating point mutations in the RET protooncogene in medullary thyroid cancer, this predominant mutation in cancers of follicular cell origin is an RET rearrangement. The RET/PTC rearrangement leads to reparative fusion of the 3′ coding region of RET to the 5′ region of another gene by virtue of their proximity [16]. These fusion genes have the ability to self-dimerize and constitutively activate downstream signal pathways through autophosphorylation of the docking sites Y905, Y1015, and Y1062 [17]. This signal is mainly mediated through the RAS–RAF–MAPK and PI3K/Akt pathways; however, alternative pathways may also exist, as in the case of Rap1, a small G protein which can mediate signals to BRAF [18].

Fusco et al. first reported the fusion of *RET* and the *H4* gene (now referred to as the RET/PTC1 rearrangement) [19]. Since then, more than 15 forms of RET rearrangement with other partner genes have been reported [3]. Among the known rearrangements, RET/PTC1 and RET/PTC3 (fusion of *RET* and the *RFG* gene) represent over 90% of RET/PTC rearrangements; others include RET/PTC2, ELKS/RET, and other rarer forms associated with radiation-induced thyroid cancers [20].

The main cause of RET/PTC rearrangements in PTC is radiation exposure. In human normal thyroid tissues transplanted into SCID mice, RET/PTC rearrangement was detected after X-ray exposure of 50 Gy [21]. Furthermore, investigations of patients with PTC associated with the Chernobyl nuclear reactor accident had a higher prevalence of RET/PTC rearrangement (up to 80%) than in PTC patients with no history of radiation exposure where BRAF

mutations are more common [22]. Nevertheless, the presence (however infrequent) of RET/PTC rearrangement in patients without known radiation exposure implies another, radiation-independent mechanism [23].

The prevalence of RET rearrangement varies from 5 to 85%, with higher rates in pediatric and irradiated patients [23–25]. Most RET/PTC rearrangements are found only in PTC; however, some investigators have found these rearrangements in Hürthle cell adenomas and Hürthle cell carcinomas (HCC) [26]. HCC is considered to be a variant of FTC by the World Health Organization, but differences in clinical behavior such as higher rates of LN metastasis and different subtypes of HCC have led many investigators to conclude that it is a separate and distinct subtype of thyroid cancer. In this light, RET/PTC rearrangements may play a role in the development of the specific papillary type of HCC as opposed to FTC.

RET/PTC rearrangements appear to be an early event in carcinogenesis of PTC, based on their presence in occult papillary thyroid cancers [27]. RET/PTC has also been shown to transform follicular thyroid cells after transfection [28]. Different types of RET/PTC rearrangements may be associated with distinct biological behaviors. Patients with RET/PTC1 usually have slow indolent cancers, whereas RET/PTC3 is found in a solid variant of PTC with a more aggressive tumor phenotype [22, 29, 30]. Nevertheless, several reports have failed to identify RET/PTC rearrangements in aggressive forms of PTC [31].

BRAF

BRAF mutation is the most frequent mutation in PTC [32]. It has recently become the subject of active investigation because of its relationship to a more aggressive clinical phenotype. It also presents new opportunities for the development of diagnostic markers and a target for therapy.

The protein product of BRAF is one of three isoforms belonging to the RAF family of serine/threonine kinases, along with ARAF and CRAF. The *BRAF* gene is located on chromosome 7q23 and encodes a 95-kDa cytoplasmic protein. It is composed of three conserved regions – CR1, CR2, and CR3. CR1 is located at the amino terminal and is thought to serve a regulatory function via its RAS-binding and cysteine-rich domains. CR2 is an activation loop with phosphorylation sites at S445 and S448 [33], and the CR3 region has a kinase domain at the carboxy terminal [34]. Activation of RAF by phosphorylation occurs immediately downstream of the membrane or cytoplasmic receptor; this phosphorylation in turn relays signals through the MAPK pathway, which plays a significant role in cell proliferation, migration, and survival [35]. After the initial report by Davies et al. of the link between the BRAF somatic mutations in exon 11 and exon 15 in human cancers [36], BRAF mutations have been identified in a wide variety of tumors such as malignant melanoma and cancers of the breast, colon, ovary, lung, and thyroid [37].

In thyroid cancers, BRAF mutations are usually confined to exon 15 in the T1799A position, which results in an amino acid change from valine to glutamate (V600E) in the kinase domain. This V600E mutation represents almost all of the BRAF mutations found in thyroid cancer. In addition to the T1799A point mutation, however, other rarer forms of BRAF mutation have also been reported, including a point mutation in A1801G [38], tandem TG1800AA mutation, AKAP8–BRAF rearrangement, G1800_1802AAdel and T1799_1801TGAdel mutation in metastatic lymph node tissue, and V599Ins mutation [39]. No germ line BRAF mutations have as yet been identified [40].

The prevalence of BRAF mutations varies from 36 to 86% in papillary thyroid cancers [38, 41–44]. Interestingly, some geographic regions and ethnic groups appear to have a higher BRAF mutation rate. In Korea, for example, reports of prevalence range from 58 to 86% [44]. BRAF mutation is found less frequently in pediatric patients with PTC, or in patients with PTC following radiation exposure. Only 4–6 % of PTCs from Chernobyl had BRAF mutations, whereas RET/PTC rearrangements occurred in 35–58%. Younger patients are also more likely, with or without a history of radiation exposure, to have RET/PTC rearrangements [45, 46]. In contrast, a BRAF mutation is much more prevalent compared to RET/PTC rearrangements in PTCs from adults with or without a history of radiation exposure [46]. Indeed, this finding has also been confirmed in older patients without radiation exposure history [47].

It is rare for BRAF, RAS, or RET/PTC rearrangement to be present simultaneously. All but one study have shown mutual exclusivity of

these mutations in PTC [46]. This represents one of the most distinctive characteristics found in genetic mutations of PTC. This mutual exclusivity suggests that a single genetic alteration may be enough to drive follicular cell transformation and the development of PTC.

The V600E BRAF mutation results in conformational change in the CR2 activation loop which leads to higher ERK1/2 kinase activity and constitutive MAPK pathway activation [48, 49]. The ability of the other forms of BRAF mutations to cause MAPK activation has not been completely elucidated, but seems likely given that the T1799-1801del and T1799-1816ins forms are in the activation loop of the protein [50]. Furthermore, the BRAF pathway also can be modulated by other signals such as FGF. For example, restoration of FGFR2 by stable transfection in PTC cell lines attenuates BRAF and MAPK phosphorylation [51].

The presence of a BRAF mutation is closely related to PTC development. Thus, Knauf et al. [52] showed development of PTC in a transgenic BRAF mutant mouse model. Furthermore, it seems that BRAF mutations play a role in tumorigenicity, growth, and proliferation of PTC, based on in vitro studies of BRAF knocked-out or inhibited cancer cell lines [53]. As mentioned previously, a BRAF mutation is the most common somatic mutation in PTC; however, it also exists in variants of PTC such as tall-cell PTC, poorly differentiated PTC, and anaplastic thyroid cancer BRAF copy number gain, as measured by fluorescence in situ hybridization, is common in FTC and follicular adenoma but not in PTC [54]. In general, more aggressive phenotypes such as tall-call variant of PTC are more likely to have a BRAF mutation than well-differentiated PTC. Recently, Trovisco et al. reported that 40% of oncocytic variants of PTC and 75% of Warthin-like variants had BRAF mutations, whereas no BRAF mutations were found in columnar variants of PTC, in diffuse sclerosing variants of PTC, or in hyalinizing trabecular thyroid tumor [38]. The absence of BRAF mutations in columnar variants seems surprising as these tumors are similar to tall-cell variants.

As mentioned above, BRAF mutation is mutually exclusive of the other main genetic changes and the most prevalent mutation in PTC [42, 43]. Some investigators have suggested testing for the BRAF V600E mutation may improve the diagnostic accuracy of FNA biopsy. BRAF mutation analysis in needle biopsy samples had a sensitivity of 37–85.3%, and specificity 100% [42, 55].

Some investigators have reported that the presence of a BRAF mutation in PTC is associated with a more aggressive clinical behavior. A BRAF mutation is associated with older age [47], extrathyroidal invasion [56], male gender [57], regional lymph node metastasis [44, 56], higher stage [56], and recurrence [44, 56]. Several investigations suggest possible mechanisms for the BRAF V600E mutation and its more aggressive tumor phenotype. Expression of thyroid-specific iodine-transfer genes, including TPO [58], sodium and iodine symporter [59], Tg [60], and pendrin [61], are decreased in BRAF mutation-associated PTC. The presence of a BRAF mutation is also associated with angiogenesis and local invasion [62], as evidenced by increased expression of MMP3/9/13 after BRAF mutant transfection [63]. The correlation between BRAF mutation and aggressive behavior is further supported by a study that demonstrated restoration of the expression of iodide-metabolizing genes in PTC cells with a BRAF mutation after suppression of the BRAF/MEK/MAPK pathway [64].

Not all investigations, however, demonstrate an association between BRAF mutation status and PTC behavior. Fugazzola et al. reported no association between BRAF mutation and aggressive behavior of PTC in a multicenter study of 260 patients [65]; there have been other studies that have supported these findings [41, 42, 66]. Possible explanations for these discordant results are study cohort size, geographic area, inclusion of nonconventional papillary thyroid cancer, methods for BRAF detection, lack of multivariate analysis, and insufficient follow-up time to determine patient outcome. A recent meta-analysis including 1,168 patients from 12 studies showed association of BRAF mutation with clinical stage and extrathyroidal invasion but did not include all the studies to date [67].

It remains unclear whether the use of a more aggressive treatment modality (such as routine prophylactic bilateral central lymph node dissection or high-dose radioactive iodine ablation) is mandated at this time for localized PTC harboring a BRAF mutation. Recently, Fagin et al. demonstrated that DUSP5 and MKP3, (MAPK pathway inhibitor enzymes) are up-regulated by BRAF activation [63]. This suggests that certain

molecular markers play a role in modulating activated BRAF signals and may influence the effect of a BRAF mutation on tumor aggressiveness. Thus, it may be possible to find molecular changes that affect prognosis in PTCs with a BRAF mutation.

NTRK Rearrangement

The *NTRK1* gene is located on chromosome 1q22 and encodes the receptor for nerve growth factor. Similar to RET, NTRK1 undergoes oncogenic activation by chromosomal rearrangement to the 5′ region of another gene. Several types of rearrangements have been reported depending on the subtype of TRK. NTRK1 is formed through intrachromosomal rearrangement with the 5′ region of the nonmuscle tropomyosin gene. TRK-T1 and TRK-T2 are formed by fusion with the *TPR* gene, while TRK-T3 is formed with the *TAG* gene [68, 69]. TRK1 rearrangements are found only in PTC and are considerably less prevalent than RET/PTC rearrangements [70].

PAX8/PPARγ Fusion

PAX8 is a transcription factor that is expressed at higher levels in follicular thyroid cells, and regulate the expression of thyroid-specific genes [71]. PPARγ is a nuclear hormone receptor and transcription factor which regulates cellular proliferation and differentiation. PAX8/PPARγ fusion is generated from chromosomal translocation t(2;3)(q13;p25). The fusion gene contains the promoter 5′ region of PAX8 along with the coding region of PPARγ. This fusion gene encodes a protein called PAX8/PPARγ fusion protein (PPFP). PPFP is found predominantly in FTC, with a prevalence of 26–63% [72, 73]. PAX8/PPARγ has been suggested to play an important role as a tumor suppressor gene by inhibiting the function of wild-type PPARγ.

Similar to the case of BRAF mutation and PTC, the possibility of PAX8/PPARγ as a diagnostic and prognostic marker for FTC has been proposed [74]. Furthermore, recent findings that PPARγ agonists can induce redifferentiation of FTC cell lines lead to intriguing ideas of possible therapeutic applications [75].

P53

P53 is one of the most important tumor suppressor genes in human malignancies, as evidenced by the finding that its inactivating point mutation is found in 50% of human cancers. The gene is located on chromosome 17p13 and encodes a 53-kDa protein product. P53 integrates multiple stress signals and regulates cell response to DNA damage by the induction of a series of target genes which attenuate cell-cycle progression. In thyroid cancer, only 10% of all thyroid cancers harbor the P53 mutation, and are most frequently found in poorly differentiated thyroid carcinomas (75%) and ATC [76, 77]. As these data imply, P53 mutations are late events in the progression from differentiated carcinoma to undifferentiated carcinoma and ATC. P63 and P73, which are transcriptionally active and inactive isoforms of P53, have also been reported to play a role in carcinogenesis of differentiated thyroid carcinoma [78].

PTEN

PTEN is a tumor suppressor gene located on chromosome 10q23.3. It encodes a tyrosine phosphatase, which serves to inactivate tyrosine kinase-mediated pathways. In thyroid tissue, PTEN mutation leads to activation of the PI3K/Akt pathway and development of FTC [79]. Inactivating germline mutations of PTEN are frequently found in Cowden's syndrome, which is characterized by hamartomas, breast cancer, thyroid cancer, and multinodular goiter. The prevalence of somatic PTEN mutations in thyroid carcinoma is low (6%), but it is present in approximately 26% of benign thyroid tumors [80].

Thyroid-stimulating hormone receptor Thyroid-stimulating hormone receptor (TSHR) is a transmembrane glycoprotein which on binding TSH functions as the primary regulator of follicular thyroid cell function. Activating TSHR mutations primarily occur in autonomous thyroid adenomas, with prevalence rates ranging from 3 to 82% [81]. TSHR mutation is rare in malignant thyroid tumors, and their role in thyroid carcinogenesis is unclear [82].

Others Molecular Factors Involved in Thyroid Cancer of Follicular Cell Origin

In addition to the above-mentioned mutations, several other genetic changes have been reported in thyroid tumors. The protein product of MET,

a receptor of hepatocyte growth factor (HGF), has been shown to be overexpressed in 75% of PTC and 25% of ATC but activating mutations have only been found in 7% of well-differentiated thyroid carcinomas [83]. Point mutation of the gene for stimulating G protein (GSP) has been reported in nonfunctioning autonomous adenomas and thyroid carcinomas, with a prevalence of 7–28% [84]. Simultaneous occurrence of RAS and GSP mutations may be associated with more aggressive behavior of differentiated thyroid carcinomas, but is rare [85]. A β-catenin mutation is only observed in poorly differentiated thyroid carcinoma (0–25%) and ATC (up to 66%) but not in well-differentiated carcinoma [86]. β-Catenin gene mutations induce nuclear localization of the β-catenin product, and may contribute to progression toward poorly differentiated carcinoma and ATC [87]. Other less well-established or less-frequent genetic changes associated with thyroid cancer include EGFR/c-erb2, APC, MTS1, Rb, cyclin D1, E-cadherin, and FGFR [8, 88].

Epigenetic Changes in Thyroid Cancer

Epigenetics refers to changes in gene expression, usually in the form of gene silencing, that occur due to processes that do not fundamentally alter genomic DNA. The term encompasses a variety of mitotically heritable mechanisms that are designed to play important roles in normal eukaryotic processes, including embryogenesis, differentiation, and genomic imprinting. Thus, derangements by epigenetic mechanisms could result in a variety of disease states, including carcinogenesis. Indeed, in the past two decades there has been a growing body of evidence that suggests that epigenetic changes, as well as their intricate association with classic genomic mutations, contribute to the pathogenesis of cancer.

There are generally thought to be three major categories of epigenetic mechanisms – DNA methylation, histone modification, and nucleosome remodeling. DNA methylation, by far the most studied and characterized, classically involves the methylation of a cytosine residue in a CpG dinucleotide-rich area (known as a CpG island) within the 5′ promoter region of a gene, thereby silencing its expression as well as that of any number of other downstream genes. Covalent histone modification occurs via deacetylation and methylation at specific lysine residues, which causes the protein to more tightly bind and compact the DNA sequence within the chromatin structure and thus prevent its ability to be transcribed. Nucleosome remodeling refers to a variety of ATP-dependent polypeptide complexes, including the nucleosome-remodeling and deacetylase complex (NuRD) and SWI/SNF that appear to have central roles in local noncovalent chromatin modification and transcriptional repression. It is important to note that the three mechanisms described above increasingly appear to intimately interact with one another to cause the permanent silencing of cancer-related genes [89].

Prior investigations studying the epigenetics of thyroid cancer have largely focused on DNA methylation but we will also briefly discuss other mechanisms.

DNA Methylation and Thyroid Tumorigenesis

There is growing evidence that DNA methylation-mediated silencing of genes is an important mechanism of thyroid carcinogenesis. Most of the silenced genes that have been studied are associated with thyroid function and tumor suppression (Table 7.2). In addition, DNA methylation has been shown to correlate with known genetic mutations that predispose to thyroid cancer [90]. *BRAF* is an example of this phenomenon. As described above, mutation in this gene can cause constitutive activation of the BRAF/MAPK pathway and the development of PTC. A recent study has shown that PTC specimens with methylated tumor suppressor genes, including *TIMP3*, *SLC5A8*, *DAPK*, and *RARβ2*, had a significantly higher percentage of *BRAF* mutations and also predicted a greater degree of clinical aggressiveness [91]. This suggests that inactivation of these tumor suppressor genes can contribute to the constitutive activation of the mitogen BRAF/MAPK pathway in PTC. This is further supported by the finding that *FGFR2*, which encodes a fibroblast growth factor receptor protein that downregulates BRAF/MAPK signal transduction, is methylated and silenced in several thyroid cancer cell lines [92].

Table 7.2. Genes involved in thyroid cell function that are epigenetically silenced by DNA methylation

Gene	Normal function of encoded protein
DAPK	Calcium/calmodulin-dependent serine threonine kinase; acts as a tumor suppressor via proapoptosis
FGFR2	Tyrosine kinase receptor that competitively binds FGF; acts as a tumor suppressor by downregulating the *BRAF*/*MAPK* pathway
NIS	Sodium/iodide symporter; transports iodide from blood into thyroid cell through basal membrane
p16	Competitive binder of CDK-4 and CDK-6; acts as a tumor suppressor by blocking cell-cycle progression at G1/S phase
PTEN	Phosphatase; acts as a tumor suppressor by dephosphorylating PIP3 with resultant downregulation of the PI3K/Akt signal transduction pathway
RARβ2	Retinoic acid receptor, acts as a tumor suppressor by regulating the growth of epithelial cells
RASSF1A	Signaling protein, acts as a tumor suppressor probably by inhibiting the Ras pathway
RIZ1	Nuclear protein methyltransferase; acts as a tumor suppressor by binding Rb
SLC5A8	Sodium/iodide symporter; transports iodide into thyroid cell through apical membrane; also acts as a tumor suppressor via proapoptosis
SLC26A4	Sodium/iodide symporter; transports iodide into thyroid cell through apical membrane
TIMP3	Tissue inhibitor of metalloproteinase via binding of Zn-binding site; acts as a tumor suppressor by inhibiting growth, angiogenesis, and invasion
TSHR	TSH receptor; binds TSH in the upstream regulation of iodide-dependent thyroid hormone formation

Other genes associated with thyroid cancer have recently been demonstrated to be methylated, including *PTEN* and *RASSF1A* [93, 94]. The case of *RASSF1A* is particularly interesting because it is a tumor suppressor gene which encodes a signaling protein that probably acts in the Ras pathway by blocking cell-cycle progression and inhibiting cyclin D1 accumulation. Suppression of its expression has been reported in a variety of solid organ cancers, including lung, breast, kidney, prostate, ovary, and colon [95]. In thyroid cancer, methylation of *RASSF1A* appears to occur throughout all subtypes of follicular epithelial cell-derived carcinomas, including papillary thyroid cancer, follicular thyroid cancer and anaplastic thyroid cancer [93, 96]. However, the pattern of its epigenetic silencing varies depending on the subtype of thyroid tumor. For example, *RASSF1A* is methylated along with *PTEN* mostly in FTC, suggesting a possible role of *RASSF1A* in the same PI3K/Akt pathway that *PTEN* would normally inhibit. On the other hand, *RASSF1A* methylation is also found (albeit uncommonly) in some papillary thyroid cancers, independent of the presence of *BRAF* mutations [96]. These findings illustrate that epigenetic events can be varied and multiple, and in combination with established thyroid oncogenes can facilitate neoplastic progression supporting the multihit model of carcinogenesis as described by Knudson [97].

Considering the myriad ways in which DNA methylation can potentially affect gene expression and progression of cancer cell development, it is interesting that studies of global 5-methylcytosine content have actually shown an overall *decrease* in genome-wide methylation [98]. This phenomenon appears to hold true in the case of thyroid cancer, based on recent quantitative immunohistochemical studies that show decreased DNA methylation in PTC and FTC samples compared with benign controls [99]. This occurs despite evidence of correlation between undifferentiated thyroid carcinoma and hypermethylation at certain distinct tumor-related CpG island promoter regions [100]. The mechanism by which local hypermethylation leads to a global hypomethylation across the cancer genome remains poorly understood as does the specific regulators of genome-wide methylation.

Other Epigenetic Mechanisms in Thyroid Tumorigenesis

The covalent modification of histones via acetylation and deacetylation plays another key role in the epigenetic regulation of gene expression. Histone deacetylase (HDAC) is responsible for freeing the histone's positively charged lysine residues at the N terminus, causing the histone to more strongly bind its associated negatively-

charged DNA. This in turn results in tighter chromatin compaction and inhibition of gene expression via blockage of DNA transcription. The importance of HDAC in gene expression has become more apparent in the last decade, especially because of its close association with DNA methylation [89]. However, the role of histone modification specifically in thyroid tumorigenesis has only recently begun to be characterized. Most prior investigations have studied the effects of HDAC inhibitors on cell-cycle regulation and thyroid-specific gene expression in thyroid cancer cell lines, suggesting that HDAC-mediated histone modification inhibits apoptosis via increased *p53* and decreased *p27* activity, and leads to loss of expression of thyroid-specific genes such as *NIS*, *TPO*, *Tg*, and *RARβ* [101, 102].

Nucleosomal remodeling via noncovalent modifications in the SWI/SNF chromatin-remodeling complex and the nucleosomal remodeling complex (NuRD) has been shown to play a key role in epigenetic gene silencing in various models of tumorigenesis, such as malignant rhabdoid tumors (MRT) and cancers of the lung, breast, prostate, and pancreas [89]. To our knowledge, there have been no studies that have specifically examined the role of nucleosomal remodeling in thyroid cancer. Further investigations regarding this possible mechanism in thyroid carcinogenesis are of interest.

Summary

Our understanding of the genetic and epigenetic changes associated with thyroid cancer pathogenesis continues to increase. Many of these genetic and epigenetic changes will have important clinical applications concerning the diagnosis, prognosis, and treatment of patients with thyroid cancer.

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8

Well-Differentiated Thyroid Cancer: An Overview and the Chernobyl Effect

Shamly V. Dhiman Amara, Robert McConnell, and William B. Inabnet

Introduction

Thyroid cancer is the most common endocrine malignancy and its incidence is increasing [1, 2]. Differentiated thyroid cancer consists of papillary, follicular, and Hurthle cell histological types. Although it typically has a good prognosis due to its long, indolent, and well-tolerated natural history, lifelong follow-up is recommended as late recurrences may occur after surgery. Advances in diagnostic modalities and pathologic analysis continue to evolve. High-resolution ultrasound plays an increasingly important role in the management of thyroid cancer, including diagnosis of malignancy, preoperative lymphatic mapping and postoperative surveillance. Surgery remains the mainstay of therapy; however, thyroid suppression and radioactive iodine ablation also contribute to the treatment. The first section of this chapter contains an overview of the clinical characteristics of well-differentiated thyroid cancer including risk factors, symptoms, diagnosis, histologic types, management and follow-up strategies. The second part will provide a more detailed evaluation of the effects of the Chernobyl nuclear accident on the subsequent development of well-differentiated thyroid cancer.

Risk Factors

The incidence of thyroid cancer continues to increase at a rate greater than that of any other cancer; approximately 7% a year [3]. Although the reason for this increase is still unknown and under investigation, several theories have been proposed, such as environmental influences and an increase in the detection of papillary thyroid cancer (PTC) less than 2 cm in diameter [4]. More frequent use of medical imaging has led to an increased detection rate of small, subclinical tumors, which in turn may explain the perceived higher incidence of differentiated thyroid carcinoma [5]. Certain risk factors may increase suspicions for thyroid malignancy. These include but are not limited to age, gender, history of childhood head and neck irradiation, familial syndromes, cytology on fine needle aspiration (FNA), presence of symptoms that indicate invasion of surrounding structures and nodule size of greater than 4 cm. Patient age is the single most important prognostic factor of well-differentiated thyroid cancer, with patients younger than age 45 years having the best prognosis. In fact, patients less than 45 years of age who have widespread metastatic disease are still classified as having stage II disease (Table 8.1). Although this disease is

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Table 8.1. Staging of well-differentiated thyroid cancer [25]

STAGE	Age <45 years	AGE > 45 years
I	Any T, Any N, M0	T1, N0, M0
II	Any T, Any N, M1	T2, N0, M0
III	Any T, N1, M0	T3, N0, M0
IV	Any T, Any N, M1	T4, N0, M0

TX: Primary tumor cannot be assessed.
T0: No evidence of primary tumor.
T1: The tumor is 2 cm (slightly less than an inch) across or smaller.
T2: Tumor is between 2 cm and 4 cm (slightly less than 2 inches) across.
T3: Tumor is larger than 4 cm or has begun to grow into nearby tissues outside the thyroid.
T4a: Tumor of any size and has grown extensively beyond the thyroid gland into nearby tissues of the neck T4b: Tumor has grown either back toward the spine or into nearby large blood vessels.
N1a: Cervical LN.
N1b: Lateral Cervical, Contralateral, Bilateral, Upper Mediastinal.
Source: Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer Science and Business Media LLC, www.springerlink.com

more prevalent in females and therefore the overall risk is higher for females, males have an increased risk of thyroid carcinoma over a lifetime [6]. The lifetime risk of being diagnosed with thyroid cancer, both males and females, is about 1% [7].

The likelihood of cancer increases sevenfold if a palpable thyroid nodule has any of the following features: firm or fixed to adjacent structures; regional lymphadenopathy; vocal cord paralysis; rapid growth; or invasion into neck structures [8]. An important risk factor for PTC is previous history of radiation exposure, especially to the head and neck region during childhood [6]. Following the Chernobyl incident of April 1986, radiation exposure, especially among children, resulted in a tremendous increase in the number of thyroid cancers, the details of which are discussed in the second portion of this chapter. Another risk factor for follicular thyroid cancer is iodine deficiency [9]. However, in the USA, a recent data analysis has indicated that the nonpregnant adult population is iodine sufficient [10].

Symptoms

Although thyroid cancer most often presents as a solitary nodule, the majority of thyroid nodules are benign. Many patients have an incidental finding of a thyroid nodule by an unrelated radiologic study or more commonly when found on routine examination by their primary care physician. The index of suspicion for cancer is highest in patients with one or more risk factors, including radiation exposure, family history of thyroid malignancy and a personal history of thyroid cancer that was treated by less than total thyroidectomy. A workup ensues appropriately with a cervical ultrasound and FNA.

Although most patients are asymptomatic, advanced or large thyroid cancers can present with noticeable symptoms that suggest invasion of surrounding structures. These symptoms can often include but are not limited to the "3 D's: dysphasia, dysphonia and dyspnea." Other signs of cancer include nodules with a hard consistency, presence of palpable nodal disease, and/or rapid growth of a nodule or mass. Other physical or radiological findings include vocal cord paralysis, fixation of the thyroid nodule, and tracheal deviation or invasion of surrounding structures [6] (Fig. 8.1). More aggressive histological subtypes may present with distant metastatic disease.

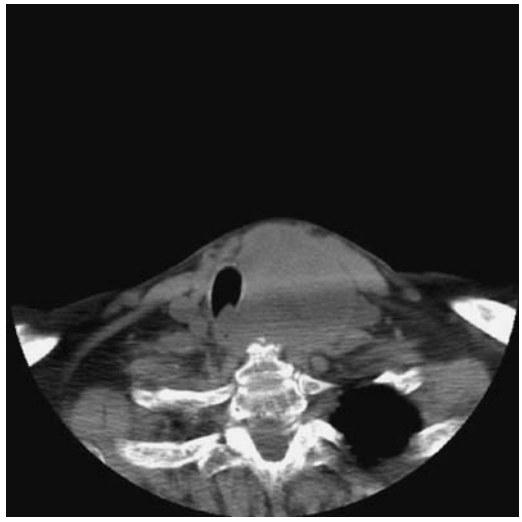

Fig. 8.1. A large papillary thyroid cancer with left sided esophageal invasion.

Diagnosis

With the increasing use of ultrasound, thyroid nodules are detected on a more regular basis. Features suggestive for thyroid malignancy can also be detected on ultrasound such as hypoechoic echotexture (86%), microcalcifications (42%) or no calcifications (47%), well-defined margins (47%), and intrinsic hypervascularity (69%) [11, 12]. Less common features include hyperechoic or mixed echo texture, cystic elements, irregular margins, hypovascularity, and coarse or peripheral calcifications [11]. Preoperative lymphatic mapping using ultrasound is a relevant development in the evaluation of patients with involved lymphadenectomy.

The diagnosis of thyroid cancers relies on FNA of thyroid nodules. A recent study suggests that an increase in the number of thyroid nodules undergoing FNA leads to an increase in the rate of surgical excision [13]. Although FNA is an accurate diagnostic test for papillary carcinomas, it cannot reliably discriminate between follicular thyroid cancers and benign follicular adenomas. For follicular tumors the diagnosis cannot rely upon FNA findings since certain histologic features such as blood vessel or tumor capsule invasion are required for a diagnosis of cancer. Although some surgeons use intraoperative frozen section to guide operative management, frozen section is not useful for follicular or Hurthle cell cancers, as the tissue processing distorts the architecture of the nodule and does not permit accurate assessment of capsular or vascular invasion [14]. Other diagnostic modalities for accurate localization and anatomic definition of disease are Computed Tomography (CT) or magnetic resonance imaging (MRI) scans of the neck and positron emission tomography (PET) scanning.

Since patients commonly undergo CT scans and PET scanning for unrelated conditions, incidental thyroid findings are frequently encountered. However, there is no indication for routine use of CT scans or PET scans to determine presence or histology of thyroid nodules. If, however, certain pathologic clinical findings are noted or metastatic disease is encountered then further investigational studies such as CT and PET scans are employed. A retrospective review from the Mayo Clinic reported focally high uptake of 18F-FDG in the thyroid as an incidental finding in 1.1% of patients and malignancy was confirmed or suspected in 17/48 (35%) of those patients that had adequate follow-up [15]. CT scanning of the neck is most helpful when local-regional invasion is suspected based on presentation and physical examination. If malignancy is strongly suspected, it is important not to use intravenous contrast during CT scanning, as the associated iodine load will delay radioactive iodine ablation by 3–4 months.

Papillary Carcinoma of Thyroid

PTC is the most common thyroid cancer, accounting for more than 80% of cancers found in iodine-rich areas. Although PTC has a favorable prognosis, it is multicentric in 35–85% of cases and lymph node metastases are found in approximately 40% of adults, and more often in children. Also the presence of psammoma bodies is evident about 40% of the time. Autopsy studies in the early 1960s and 1970s demonstrated that 80% of clinically relevant PTCs will have microscopic contralateral lobe involvement, and up to 80% will have microscopic foci in ipsilateral lymph nodes [16, 17].

Local recurrence can be frequent; and recent literature has advocated a more aggressive surgical approach so that mortality rates related to locoregional recurrence are reduced [18]. However, external radiotherapy improves local failure free survival in patients with pathologically confirmed positive resection margins and reduced local failures in patients with T4 disease [18]. Consensus guidelines recommend total thyroidectomy rather than thyroid lobectomy to treat potentially multicentric disease, to insure maximal uptake of adjuvant radioactive iodine, and to facilitate posttreatment follow-up by monitoring serum thyroglobulin (Tg) levels [19]. The follicular variant of PTC (FVPTC) has characteristics similar to those of the classical variety. Similar tumor characteristics between classical and follicular variant of PTC exist in terms of tumor size, presence of multifocality, capsular invasion, lymphovascular permeation, and perineural infiltration. However, FVPTC patients have significantly fewer histologically confirmed cervical lymph node metastases and extrathyroidal involvement [20].

Another type of PTC is the tall cell variant (TCV) of papillary cancer, representing 1–5% of all thyroid cancers. The TCV of PTC is typically more aggressive than classic PTC and often presents with involved local lymph nodes (Fig. 8.2A, B). Other clinical characteristics include older age at presentation, larger tumor size, and high frequency of extrathyroid tumor extension [21]. General consensus for treatment of TCV is total thyroidectomy. Another subtype of PTC is the aggressive insular type. This type of tumor is defined as well differentiated yet contains islands of poorly differentiated cells and requires total thyroidectomy.

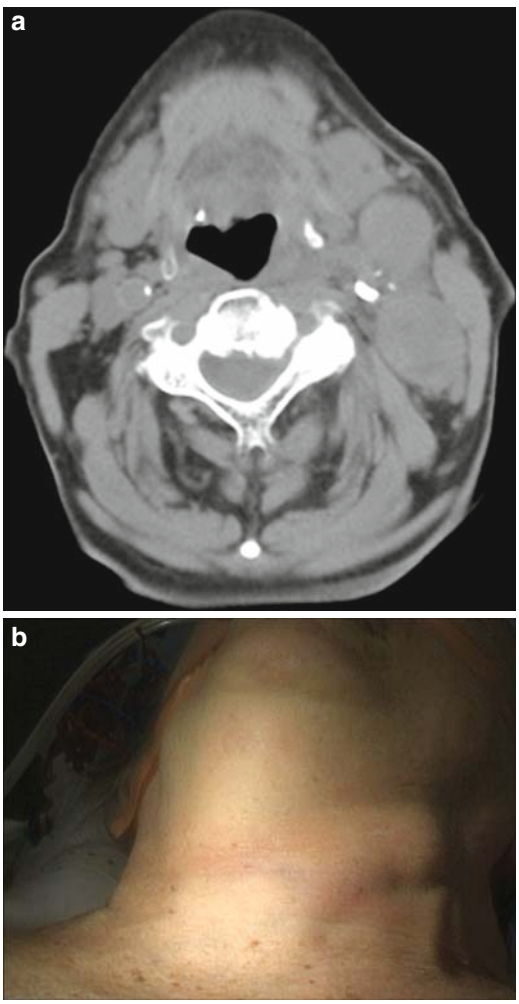

Figure 8.2. (**A**, **B**) CT Neck demonstrating tall cell variant of papillary thyroid cancer with extensive adenopathy.

Further debate exists regarding extent of lymph node dissection for PTC. Options for treatment of palpable and involved lymph nodes depend on the location and extent of involvement: central versus modified lymph node dissection and routine versus selective dissection. During a central lymph node dissection, level VI nodes are resected en bloc. The borders for a level VI dissection include the hyoid bone superiorly, the sternal notch inferiorly, and the carotid artery laterally and should also include the paratracheal or 'Delphian' lymph node. Adenopathy may also be located lateral to the sternocleidomastoid muscle. In these instances it is standard of care to complete a modified radical neck dissection in which levels II [(upper jugular chain), III (middle jugular chain), IV (lower jugular chain) and V lymph nodes are removed, sparing the sternocleidomastoid muscle, internal jugular vein, and spinal accessory nerve (cranial nerve XII)]. Two schools of thought exist concerning routine central node dissection versus selective dissection of only involved nodes. One recent study advocated a formal central compartment dissection for PTC not based on patient gender or age but on large tumor size and multifocal disease [22]. Recently, measurement of Tg in the wash out of the needle (FNAB-Tg) has been proposed for early detection of neck lymph node metastasis in patients with differentiated thyroid cancer [23]. Other types of node dissection used include selective neck dissection, modified radical neck dissection, and routine cervical lymph node sampling with modified radical neck dissection in patients with metastatic carcinoma evident on frozen section, and aggressive "compartment micro-dissection."[24]

Follicular Carcinoma and Hurthle Cell Carcinoma

FNA is far less able to discriminate follicular and Hurthle cell carcinomas from benign adenomas, because the diagnostic criterion for these malignancies requires histological demonstration of vascular or capsular invasion [25]. Surgical biopsy is advisable, because approximately 20% of all such lesions are follicular carcinomas [25]. The World Health Organization classification considers Hurthle cell

Table 8.2. Features of papillary and follicular thyroid cancer

	Papillary CA	Follicular CA
Percent of total	80%	10–20%
Predominant Age	3–5th decades	5–6th decades
Clinical pathology	Nonencapsulated, sharp circumscribed	Larger, Encapsulated, Noncystic
Microscopic pathology	Papillary fronds of epithelium, 50% calcified deposits (Psammoma bodies)	Capsular and Vascular invasion
Spread	Lymphatic	Hematogenous
Main risk factor	Previous radiation exposure, family history	Iodine deficiency
Cervical Lymph Node Metastases	More common	10% at initial presentation Distant Mets: 33% Lung and Bone
10-Year Survival	80–95%	70–95%

carcinoma as a variant of follicular carcinoma [26]. This variant is rare, has a worse prognosis, and has a more frequent tendency for cervical lymph node metastases. Although most management options are the same for follicular and Hurthle cell carcinomas, metastatic Hurthle cell is less likely to concentrate ^{131}I [25]. It is well documented that both follicular and Hurthle cell carcinomas have an increased chance (10%) of local–regional invasion. It is important to note normal cellular biology of the thyroid gland so the cytologic examination will not skew the diagnosis; for example, the finding of Hurthle cells on FNA is not diagnostic for malignancy and may also be found in Hashimoto's thyroiditis or Graves' disease. Multicentricity is not restricted to papillary cancers because follicular tumors are multicentric in up to 23% of cases [27]. Differences between papillary and follicular carcinoma are delineated in Table 8.2.

Operative Management

Today's consensus is that patients with high-risk thyroid cancer, such as those whose histology is poorly differentiated, with vascular, neural, or capsular invasion should undergo total thyroidectomy at initial operation. Except for minimally invasive follicular thyroid carcinoma (minimal capsular invasion with or without vascular invasion) and occult papillary microcarcinomas, debates regarding lobectomy versus total thyroidectomy for differentiated thyroid cancer in low-risk patients seem to be waning, as total thyroidectomy has been shown to improve disease-free survival and reduce recurrence rates [28–30]. The American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons have recommended near-total or total thyroidectomy as the initial procedure of choice for well-differentiated thyroid cancer [31, 32]. Total thyroidectomy greatly facilitates the use of radioactive iodine ablation and Tg during follow-up [31]. The extent of surgery may also be influenced by surgeon experience. High-volume surgeons (>100 thyroid procedures/year) are more likely to operate on patients with cancer and have the shortest length of stay and lowest complication rate [33]. High-volume surgeons have two-thirds fewer complications when treating thyroid cancer [33]. Surgical treatments are summarized in Table 8.3.

Overall Prognosis

Classification for staging both papillary and follicular thyroid cancer is shown in Table 8.3. In the USA, the 10-year overall relative survival rates for patients with papillary, follicular, and Hurthle cell carcinoma was 93, 85, and 76%, respectively [34]. Avoiding delays in diagnosis as well as an accurate and precise follow-up is crucial to assure optimal patient care.

Differentiated Thyroid Cancer: The Chernobyl Effect

The Chernobyl Nuclear Power plant accident in April 1986 exposed the residents of southern Belarus, northern Ukraine, and the southwestern

Table 8.3. Surgical strategy for well-differentiated thyroid cancer

	Current accepted surgical treatments
Papillary CA	Total thyroidectomy
Tall Cell	Total thyroidectomy
Insular	Total thyroidectomy
Columnar	Total thyroidectomy
Follicular	Lobectomy if benign adenoma or minimally invasive cancer Total thyroidectomy if angioinvasive or widely invasive follicular carcinoma on frozen section or final pathology
Hurthle Cell	Total thyroidectomy

Russian Federation to massive amounts of radioactive isotopes of iodine, mainly ^{131}I that was ingested as contaminated milk. The most important public health consequence has been an enormous increase in thyroid cancers, primarily of the papillary subtype, among those who were exposed as children [35, 36]. Although it was an enormous social and environmental disaster [37], Chernobyl provides a unique opportunity to quantify the risk of thyroid cancer following exposure to radioactive iodine [38], which is widely used in thyroid diagnosis and therapy.

Although three early, case–control studies suggested a relationship between estimated radiation dose after Chernobyl and thyroid cancer [39–41], it was only recently that a large Ukrainian cohort study found a strong, positive, approximately linear increased risk with radiation doses that were obtained shortly after the accident [42]. This study also found that the oncogenic effects of childhood exposure to radioactive iodine were not appreciably different than those of external irradiation, a widely recognized risk factor for thyroid cancer [43].

Because their thyroid gland was small and they consumed more milk, children were estimated to have received doses that were many times higher than adults [44]. Since the child's thyroid was also very sensitive to radiation [45, 46], there was considerable concern about thyroid cancer as a consequence of the catastrophe. Beginning in 1990, only four years after the accident and an extremely short latency, a dramatic increase in the number of thyroid cancers, largely of the papillary subtype, was observed among younger children from the most heavily contaminated regions (Table 8.4) [43, 44, 47]. Although there was legitimate concern that the increasing incidence might be a consequence of intensive screening, about 75% of the excess risk was estimated to be radiation exposure [48–50]. By 1994 almost 300 cases had accumulated in the three most heavily contaminated areas. In the Gomel region of Belarus, located immediately adjacent to the plant, there was an almost 200-fold increase in the number of childhood thyroid cancers during the decade spanning the accident.

There were a number of notable differences between these post-Chernobyl cancers and sporadic pediatric cancers in the USA and Europe [51–54]. One was the large number of younger children in the former Soviet states (Table 8.5). In Ukraine, a total of 426 cases in children less than 15 years of age had accumulated in the first decade after the accident. In the other countries, a comparable number of cases were collected over a very much longer period of time, and from a much larger population. For example, the 154 cases from the UK occurred over three decades. About one half of the exposed children were less than 10 years of age, while in the other countries only one quarter to one third were of this age group, suggesting a shift to younger ages in the radiation-exposed group.

Table 8.4. Pediatric thyroid cancer in territories contaminated by the Chernobyl accident (April 1986) during three different time periods before and after the accident

	1981–1985		1986–1990		1991–1994	
	No. of cases	Rate*	No. of cases	Rate*	No. of cases	Rate*
Gomel, Belarus	1	0.5	2.1	10.5	143	96.4
Northern Ukraine	1	0.1	2.1	2.0	97	11.5
Russian Federation	0	0	3	1.2	20	10.0

*Number of pediatric thyroid cancers per million population.

Table 8.5. Age of onset of pediatric thyroid cancer in five different countries

Age (yr)	Ukraine [51]	USA [52]	UK [53]	Italy and France [54]
<4	0%	0%	7%	2%
4–9	47	23	22	38
10–14	53	69	71	69
Number	125	71	154	134

Another difference between exposed and unexposed children was the gender ratio. In adults, differentiated thyroid cancer is far more common in women than in men, and in unexposed pediatric populations, younger children have a lower ratio than do older children [55]. In contrast, in both Belarus and Ukraine the gender ratio varied between 1 and 2 regardless of age, roughly that expected in a prepubertal unexposed population [51, 54]. Therefore, radiation exposure appeared to blunt the rise in the gender ratio that normally happens with advancing age.

The early surgical experience suggested that the cancers found among exposed children demonstrated high rates of extrathyroidal extension, locoregional and pulmonary metastases, and postoperative recurrence [47, 54, 56]. Compared to pediatric cancers in Europe, they were more often PTCs, occurred in younger children, had a lower gender ratio, and were generally more aggressive (Table 8.6). In addition, the post-Chernobyl carcinomas were more often associated with autoimmune findings, such as elevated serum thyroid autoantibodies and lymphocytic infiltration of the thyroid gland [54]. As experience was gained with multifocal and widespread disease, the completeness of initial surgery evolved from an early reliance upon lobectomy or subtotal thyroid gland resections to total thyroidectomy with unilateral and bilateral neck resection, completion thyroidectomy, and postoperative radioactive iodine ablation [56–58].

The histology of the papillary cancers also differed from those seen in western countries. The majority was notable for an unusual solid or solid-follicular growth pattern, characterized by solid sheets of thyroid follicular cells separated by bands of fibrous tissue [51, 56, 59, 60]. Although solid variants also occur among unexposed children, they do so at younger ages and at lower frequencies [53]. Recent pathomorphologic studies have linked the solid subtype among the radiation-exposed group to shorter latency regardless of age at exposure, whereas longer latency is characterized by a more typical papillary architecture [60, 61]. This observation suggests that the pathology of the Chernobyl cancers may be changing with increasing time since the accident [61].

Research into the molecular biology underlying the post-Chernobyl papillary thyroid carcinoma epidemic has largely focused upon activation of the *RET* (rearranged during transfection) gene through radiation-induced chromosomal reordering to form the RET/PTC protooncogene [62–66]. Under normal circumstances, RET codes for a cell-surface tyrosine kinase receptor that regulates growth, development, and survival of neural crest cells, but is not expressed in thyroid follicular cells. However, double-strand DNA breaks generated by radiation exposure can produce chromosomal rearrangements that fuse the tyrosine kinase domain of RET to portions of various other genes, creating the chimeric RET/PTC oncogenes, resulting in gene products that are constitutively active, ligand-independent

Table 8.6. Post-Chernobyl pediatric thyroid cancers compared to spontaneous cancers in Italy and France

	Belarus [54]	Ukraine [56]	Italy and France [54]
% <14 yrs	78.8	87.0	42.6
F/M ratio	1.6/1	1.3/1	2.5/1
% PTC	93.9	93.1	82.1
Extrathyroid, %	49.1	54.8	24.9
Lymph nodes, %	64.6	57.3	53.9
Distant metastases, %	7.8*	14.5†	17.3†

*Distant metastases diagnosed by chest X-ray.
†Distant metastases diagnosed by chest X-ray and ^{131}I whole-body scan.

receptor tyrosine kinases [67–69]. Although at least 11 RET/PTC rearrangements have been reported, the most common rearrangements, also found in the majority of post-Chernobyl papillary carcinomas, are RET/PTC 1 and RET/PTC 3, the latter linked to the aggressive solid-follicular subtype [66, 69]. RET/PTC is found in between 20 and 40% of unexposed adult papillary cancers, but in up to 80% of post-Chernobyl disease [62–65, 70]. However, recent experience suggests that the frequency of RET/PTC may be falling with longer latency [71].

Because of its known effect upon thyroid physiology, iodine has been considered as a possible modifier of radiation-related risk, either by affecting the dose delivered at exposure or by modulating the response to the dose received. There is a long history of iodine deficiency in the territories affected by Chernobyl.[72] Although the introduction of iodized salt during the 1950s leads to a significant decline in the goiter rate, less importance was being placed on salt iodization at the time of the accident [73]. However, coincident with the rise in the number of thyroid cancers during the 1990s, renewed attention was given to iodine nutrition [73]. Studies in children suggested a mild to moderate deficiency throughout the country, although the Gomel region may have been less severely affected than other areas of the country [74]. Mandatory salt iodization programs in Belarus and Ukraine during 2000–2001 have partially addressed this problem, and there is reliable evidence that iodine nutrition is now improving [75].

An ecological study carried out in the Brynask region of southwestern Russia found an inverse relationship between regional iodine excretion and the risk of thyroid cancer, a finding subsequently confirmed by research in Belarus that estimated soil iodine at the time of the accident [41, 76]. However, work from Ukraine found no association with iodine excretion at the time of screening [42].

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9

Poorly Differentiated and Undifferentiated Thyroid Cancer

Anthony J. Chambers and Janice L. Pasieka

Introduction

Thyroid carcinoma in its differentiated form is associated with an excellent long-term prognosis, with surgical resection and the use of radioactive iodine providing effective treatment and cure in a high proportion of patients. In contrast to well-differentiated thyroid cancer (WDTC), poorly differentiated forms of thyroid cancer exist which are associated with a more aggressive clinical course and a correspondingly less favorable prognosis. At the extreme of the spectrum of differentiation of thyroid cancers, undifferentiated (anaplastic) thyroid cancer (UTC) is one of the most biologically aggressive and lethal of human malignancies, displaying rapid invasive growth and early metastatic dissemination. It is recognized that some thyroid cancers display a degree of differentiation and biological behavior which is intermediate between WDTC and UTC in this spectrum, and this group has been referred to as poorly differentiated thyroid cancer (PDTC).

Poorly Differentiated Thyroid Cancer

In contrast to more differentiated forms of thyroid cancer, PDTC possesses a tendency for local invasion beyond the capsule of the thyroid, recurrence after surgical resection and metastatic dissemination, and as such is associated with a worse prognosis. PDTC displays a degree of differentiation on histology which lies on the spectrum between the well-preserved differentiation of WDTC and the anaplastic features of UTC. In PDTC, the characteristic follicular or papillary appearance of WDTC is not present, instead less differentiated growth patterns are observed. The classification of thyroid cancer as PDTC remains poorly defined. The most recent World Health Organization classification of thyroid tumors does not provide a criteria for categorization of PDTC, yet biologically there appears to be thyroid tumors that behave more aggressively than WDTC [1]. Until recently, there has not been agreement among pathologists in the classification of PDTC. A recently published diagnostic criteria for PDTC based on tumor histology has been proposed after review of 83 cases at a consensus meeting of thyroid pathologists in Turin, Italy [2]. In this classification, variants of follicular and papillary thyroid cancer which display more aggressive behaviors such as the columnar cell, tall cell, solid, and diffuse-sclerosing variants of papillary thyroid cancer are not considered PDTC [3]. PDTC is characterized by (1) the presence of an insular, solid, or trabecular pattern of growth on histology, (2) the absence of nuclear features of papillary carcinoma, and (3) the presence of one or more of the following features: convoluted nuclei, three or more mitoses per 10 high-power fields or foci of tumor necrosis [2]. PDTC with a predominantly

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insular growth pattern on histology has been referred to as insular carcinoma and represents a distinct variant of thyroid carcinoma which cannot be clearly related to follicular or papillary carcinoma, with an aggressive behavior and prognosis which lie between those of WDTC and anaplastic cancers [4].

Insular Carcinoma

Insular carcinoma is an aggressive form of thyroid malignancy and accounts for 3–6% of cases of thyroid carcinoma [5–7]. It occurs more commonly in females with a female to male ratio of 2:1 [4, 6, 8]. The mean age of onset is 51–57 years, with a range from 11 to 79 [4, 6–8]. Most patients with insular carcinoma present with symptoms of an enlarging mass, with 8% presenting with symptoms related to metastatic disease [4, 7]. In 27–60% of cases, the tumor develops within a preexisting goiter [6, 7]. Insular carcinomas have generally reached a large size by the time of presentation, with a mean of 5–6 cm [6, 8, 9]. Extrathyroidal invasion of the cancer into adjacent soft tissues and anatomical structures occurs in 69% at the time of presentation, including the trachea or larynx in 15% of cases [10]. Spread to regional lymph nodes may be apparent in 20–44% of patients at presentation and distant metastases in 8–67% [4, 9–11]. Distant metastatic spread occurs in 32–85% of patients, most frequently to the lung (61%) or bony skeleton (50%) and less commonly to the liver (11%) [4, 7–11].

Fine needle aspirates from insular lesions are diagnostic in most cases, with features typical of high-grade follicular neoplasms [12]. Aspirates are generally hypercellular with minimal colloid, and cytopathology characteristically demonstrates numerous round to oval pleomorphic follicular cells with scant eosinophilic cytoplasm and uniform nuclei, arranged in small nests or as individual cells [12–14].

Insular carcinomas are solid tumors with a pale coloration, and regions of hemorrhage and necrosis within the tumor substance are commonly present. The histological appearance of these tumors was first characterized by Carcangiu, who described tumor cells forming large, well-defined nests, separated from surrounding tissue by prominent clefts [4]. Tumor cells are uniform, small, and rounded in appearance with a scant eosinophilic granular cytoplasm (Fig. 9.1) [9]. In contrast to UTC, cells display minimal pleomorphism, and tumor giant cells and multinucleated cells are not identified. The tumor cells have nuclei which can appear optically clear and resemble those of papillary cancer, but nuclear overlapping and other features of papillary cancer are not present. Cells can be arranged in characteristic nests, in solid sheets of cells or in a trabecular pattern, and can form small follicles [4, 6, 9, 15]. The tumors can display a predominantly insular growth pattern or can contain mostly trabecular or solid arrangements [9, 16]. Mitoses are identified frequently throughout the tumor and occur to a variable extent. Areas of necrosis are commonly present and invasion of vascular structures is seen in 44–100% of

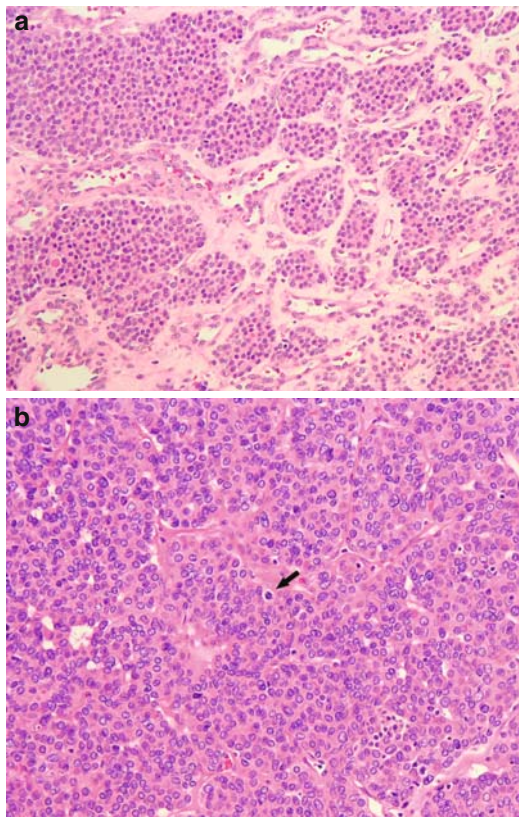

Fig. 9.1. (**A**) Photomicrograph of poorly differentiated thyroid cancer with an insular growth pattern. Insulae contain relatively uniform cuboidal cells with scant eosinophilic cytoplasm and minimal pleomorphism. Nuclear features of papillary thyroid cancer are absent. (20× magnification). (**B**) Poorly differentiated thyroid cancer with solid and trabecular growth patterns. A mitotic figure is present (*arrow*) (20 × magnification).

tumours [4, 6, 9, 15]. Immunohistochemistry is useful in the characterization of these tumors. Staining for thyroglobulin is positive in almost all cases confirming the follicular cell origin of the tumors [4, 9, 15]. Stains for keratin are positive in 75% of cases, and negative staining for calcitonin enables differentiation of these tumors from medullary thyroid carcinoma.

Pathogenesis of Poorly Differentiated Thyroid Cancer

Regions of WDTC are present in the resection specimens of insular carcinoma and other PDTC in 59% of cases, and PDTC can be found in association with 13% of UTC, suggesting that PDTC represents a step in the progression and transformation from WDTC to UTC. Genetic studies of WDTC, PDTC, and UTC using comparative genomic hybridization have shown a progressive accumulation of chromosomal abnormalities from differentiated to undifferentiated forms [17]. Tissue microarray identification of four candidate gene mutations found a similar progressive increase in mutations occurring among WDTC, PDTC, and UTC providing further evidence that PDTC may represent an intermediate stage in dedifferentiation [18]. The tumor suppressor gene p53 may be involved in this process, as mutations are present in 32% of UTC and 12% of PDTC and rarely occur in WDTC [18].

Management and Outcomes of Poorly Differentiated Thyroid Cancers

PDTC is uncommon in comparison to WDTC, and fewer studies exist which examine the role of surgical and adjuvant treatments of this disease. In contrast to WDTC, multimodality treatment with a combination of aggressive surgical resection or debulking, radioactive iodine, and external beam radiotherapy may be indicated to achieve local control of the tumor [3]. In the initial description of insular PDTC from a series of 25 patients at the University of Florence, surgical resection was performed in 24 cases of which 20 were total or near-total thyroidectomies. This was combined with formal lymph node dissection in seven cases, and external beam radiotherapy was given postoperatively in two cases. The mortality during the 8-year period of follow up of these patients was 56%, with 84% of cases developing locoregional recurrence or disseminated disease. Recurrent disease in the neck developed in 50% of patients who underwent thyroid lobectomy and in 42% of those who underwent total thyroidectomy. Surgical resection by total or near-total thyroidectomy was performed for 20 of 22 patients managed at the Queen Mary Hospital in Hong Kong, and this was combined with postoperative external beam radiotherapy in eight cases [7]. Forty-two percent of patients survived greater than 10 years, with disseminated metastatic disease developing in 32%. Postoperative radiotherapy to improve locoregional control has been recommended for PDTC due to the high incidence of extrathyroidal invasion, regional lymph node involvement, and locoregional recurrence, particularly when resection has been macroscopically incomplete [3]. The actual benefit of external beam radiotherapy in this setting is not known. In a study which collectively reviewed the outcomes after treatment of previously published case series of insular PDTC, external beam radiotherapy was not associated with an improvement in survival [8]. Given the high rate of local recurrence of PDTC, however, it is reasonable to recommend postoperative external beam radiotherapy to maximize the chance of maintaining locoregional control.

In contrast to UTC, which is rarely capable of organifying iodine, uptake of ^{131}I has been shown in more than 80% of PDTC and can be effective in the treatment of local and disseminated disease [9, 19]. Although the response to treatment of PDTC is poor compared to that of WDTC, [6, 10] and treatment with radioactive iodine was not associated with a survival advantage in two studies examining its role, ^{131}I should be given to all patients with PDTC postoperatively because of the potential benefit and lack of morbidity associated with this treatment [3, 6, 8, 10]. In patients with tumors capable of taking up iodine, whole-body scanning with radioactive iodine can detect distant metastases. Positron emission tomography with F18-fluorodeoxyglucose in patients with PDTC shows uptake of the isotope in most cases and has been used in the assessment of metastatic disease where tumor does not take up radioactive iodine [20, 21].

In a large study of 183 cases of PDTC demonstrating an insular histology from the University of Turin, a 5-year survival rate of 85% and 10-year survival of 67% was found [6]. Patients greater than 45 years, the presence of necrosis within the tumor, and higher numbers of mitoses on histology were associated with a worse prognosis. In the review combining the results of previously published series of insular PDTC, a 5-year survival of 72% and 10-year survival of 52% were calculated [8]. Patients older than 45 years and the presence of disseminated disease were associated with a higher mortality in this study. Although supported by level IV evidence only, aggressive surgical resection followed by ^{131}I and external beam radiotherapy for locoregional control appears to offer the best chance of long-term survival for patients with PDTC [3]. Systemic therapy should also be considered within a study protocol because of the high likelihood of developing disseminated metastatic disease.

Undifferentiated (Anaplastic) Thyroid Cancer

Undifferentiated (anaplastic) thyroid carcinoma is one of the most aggressive forms of cancer seen in humans and fortunately represents only a small proportion of malignancies of the thyroid gland. In sharp contrast to differentiated forms of thyroid cancer, anaplastic cancer is characterized by aggressive local invasion and early widespread metastatic dissemination, with few patients surviving longer than 12 months after presentation [22]. Local treatment with surgical resection and external beam radiotherapy and single modality systemic chemotherapy have limited roles in the management of UTC in achieving palliation and prolonging survival. The rarity of this disease has made it difficult to study.

Clinical Features

UTC is an uncommon form of thyroid malignancy, accounting for only 1.7% of all thyroid cancers recorded in the National Cancer Database of the American Cancer Society [23]. Studies from the large Surveillance, Epidemiology and End Results Program (SEER) cancer registry database of the National Cancer Institute showed no change in the incidence of UTC from 1973–2002 [24]. UTC occurs most commonly in the elderly, with a peak incidence seen in the seventh decade of life and a mean age of presentation between 65 and 75 years [22, 25–28]. It is rarely seen in patients younger than 40 years, and the mean age at presentation is considerably higher than that seen in differentiated thyroid cancers. Females are overrepresented in most series of UTC, with reported female to male ratios of 1.5:1 to 2:1 [22, 25–28]. Few risk factors have been associated with UTC. A higher incidence in iodine-deficient areas and regions of endemic goiter has been found in some studies but not in others [29–31]. A history of irradiation of the head and neck may be seen in up to 10% of patients and a causal relationship has been suggested [27, 32–37]. UTC occurring following radiation exposures tend to occur at a younger age than is normally observed, and has a mean latency period of 27 years postexposure [34].

Most patients with UTC present with symptoms related to a rapidly enlarging neck mass, accounting for 70–99% of presentations [22, 27, 28, 37–39]. In 10–29% of patients, enlargement of a previously stable goiter is the presenting feature [27, 37, 38, 40, 41]. A smaller proportion of patients may present with symptoms related to distant metastases (3–10%) or with systemic features such as weight loss [22, 27]. Symptoms had been present for a mean duration of 1 month prior to presentation in some studies [28, 38]. The size of the mass and its rapid growth are frequently associated with symptoms of compression of the airway, upper aerodigestive tract or vascular structures with stridor, difficulty in breathing, dysphagia, evidence of superior vena cava obstruction or voice change noted in up to 51% of patients at presentation [27, 28, 37, 38]. Voice change when present may be due to the effects of local compression or to involvement of the recurrent laryngeal nerve by direct tumor invasion. Acute upper airway compromise may be the mode of presentation in 18% of cases [38].

Few patients with UTC present at an early stage of disease, and in most cases this is where small foci of UTC is discovered within a larger differentiated thyroid cancer or found incidentally at thyroidectomy performed for alternate indications [28, 41, 42]. Only 8% of patients with

anaplastic carcinoma in the SEER database had disease confined to the thyroid gland at presentation [25]. Local invasion beyond the thyroid capsule is seen in greater than 82% of cases, involving surrounding structures including overlying strap muscles, the trachea and larynx, esophagus, common carotid artery, adjacent nerves, great vessels of the superior mediastinum, and overlying skin [22, 37–39, 41]. A study of adjacent structures involved by UTC found recurrent laryngeal nerve involvement in 59%, trachea or larynx in 50%, esophagus in 23%, carotid artery in 16%, and skin in 7% [39]. Direct invasion of structures within the superior mediastinum can produce superior vena cava syndrome in a small number of cases (Fig. 9.2) [28, 37, 40]. Metastatic involvement of regional lymph nodes can be documented in 21–38% of patients at presentation and is seen in 83% of cases at autopsy [25, 37, 38]. Hematogenous dissemination of the tumor to distant sites can be demonstrated in 43–64% of patients at the time of initial assessment and is present in 87% of cases at autopsy [22, 25, 27, 28, 38, 43, 44]. The most common site of metastatic spread is to the lungs, seen in 75–88% of patients with metastatic disease [27, 28, 37, 44]. Less common sites of metastases include the boney skeleton, brain, adrenal glands, and nonregional lymph nodes [22, 27, 28, 37, 43, 44].

A staging system for UTC was developed by Aldinger at the MD Anderson Cancer Center in a study of 84 patients [40]. In this study, it was found that patients with UTC confined to the thyroid (stage I) had a favorable prognosis in comparison to patients with extracapsular invasion or metastatic spread. The majority of patients with UTC fall into stages III and IV at presentation. Within the TNM classification of thyroid cancers of the American Joint Committee on Cancer, all anaplastic thyroid cancers are designated as T4, stage IV disease due to the poor prognosis of patients with this malignancy [45].

Pathology

UTC present as large, bulky masses arising from the thyroid gland. Macroscopically, these tumors have a pale, white, or tan appearance on sectioning and are firm or hard on palpation (Fig. 9.3) [46–48]. Areas of hemorrhage, necrosis, and cystic degeneration within the tumor substance are frequently apparent and the tumor may also contain regions of calcification [46, 48]. The tumor commonly displays indistinct margins with invasion into the adjacent residual thyroid parenchyma, which may

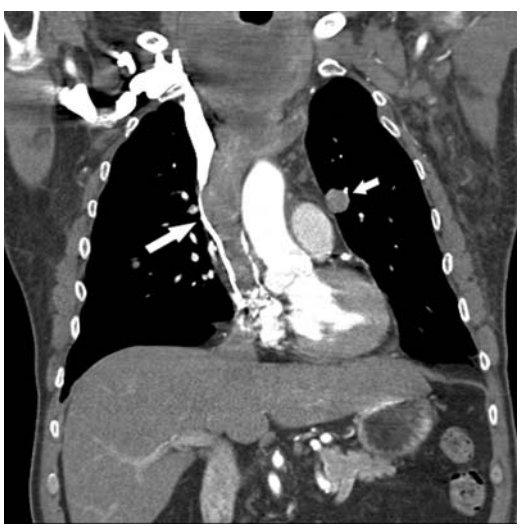

Fig. 9.2. Computed tomography of the thorax of a patient with undifferentiated thyroid cancer presenting with superior vena cava syndrome. Invasion and tumor extension within the right brachiocephalic vein and superior vena cava toward the right atrium is demonstrated (*large arrow*). A pulmonary metastasis is also present (*small arrow*).

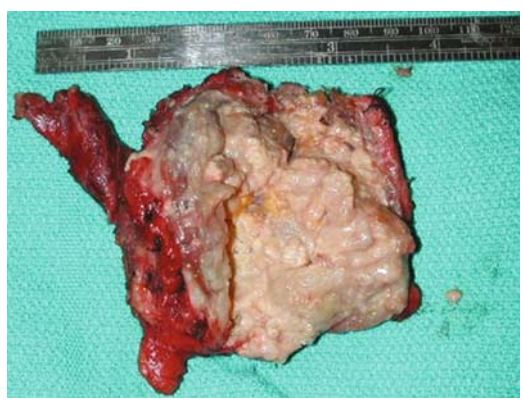

Fig. 9.3. Postresection specimen showing replacement of the left lobe of the thyroid by undifferentiated thyroid cancer. The specimen has been sectioned to demonstrate a bulky pale tumor mass infiltrating the substance of the thyroid gland with areas of necrosis and hemorrhage. The mass was resected in continuity with the overlying strap muscles which were invaded by the tumor (seen to the *left* of the specimen).

appear normal or contain evidence of preexisting nodular disease [47]. Extracapsular invasion of the tumor into surrounding structures in also commonly observed.

The histological appearance of UTC varies considerably among cases, and criteria for histological diagnosis have been defined by the World Health Organization [1, 49]. Three histological patterns are commonly identified: giant cell, spindle cell, and squamoid cell types (Fig. 9.4) [46–48]. In the giant cell form, large rounded neoplastic cells are seen with abundant eosinophilic cytoplasm, which display bizarre arrangements of hyperchromatic nuclei or be multinucleated. In the cases where spindle cells predominate, elongated fusiform cells with hyperchromatic nuclei form fascicles, often with a dense collagenous stroma, and the appearance can resemble that of sarcoma. Squamoid cellular patterns are seen less commonly than giant and spindle cell forms, and display flattened cells with abundant eosinophilic cytoplasm that form tumor nests and islands that resemble squamous carcinoma. It is rare for one pattern to predominate within a tumor, with most cases of UTC containing regions of varying histological appearance. In all forms, tumor cells have a high mitotic rate and frequent mitoses are demonstrated within sections. Large multinucleated cells resembling osteoclasts may also be seen scattered in some tumors [47]. Areas of necrosis and hemorrhage within the tumor substance are common, and there is frequently an inflammatory cell infiltrate within the stroma. In all cases, UTC displays a distinct propensity for metastasis, with areas of invasion into vascular structures and lymphatic channels routinely identified in specimens. Histological variants of UTC have also been described and display similarly aggressive tumor behavior and poor prognosis. In the paucicellular variant of spindle cell UTC, prominent fibrosis is seen with few atypical spindle-shaped cells seen within a dense collagenous stroma with scattered inflammatory cells [47, 50]. This lack of cellularity makes diagnosis by fine needle aspiration (FNA) difficult, and the histological appearance can closely resemble Riedel's thyroiditis [50]. An angiomatoid variant of UTC has also been reported and occurs very rarely, with histological features similar to angiosarcoma but with

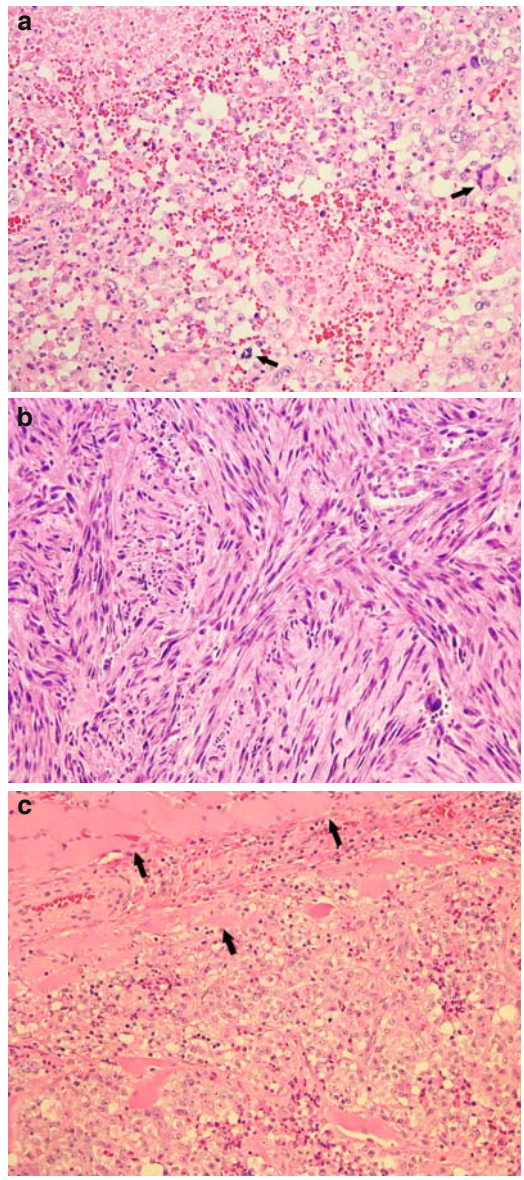

Fig. 9.4. (**A**) Photomicrograph of undifferentiated thyroid cancer of giant cell type. Large poorly cohesive cells with pleomorphic nuclei are seen in a haphazard arrangement. Areas of hemorrhage and necrosis are prominent. Mitotic figures and multinucleated giant cells are shown (*arrow*) (20× magnification). (**B**) Undifferentiated thyroid cancer with spindle cell growth pattern. Elongated fusiform cells are haphazardly arranged in fascicles with a collagenous stroma. Cells demonstrate hyperchromatic pleomorphic nuclei (20× magnification). (**C**) Undifferentiated thyroid cancer with invasion into adjacent strap muscle (*arrows*) (20 × magnification).

immunohistochemical staining consistent with a thyroid follicular cell origin [51].

UTC can closely resemble lymphoma, poorly differentiated medullary carcinoma, sarcoma, and some metastatic lesions to the thyroid both clinically and in histologic appearance. These malignancies must be differentiated from UTC as their treatment and prognosis are very different. Primary lymphoma of the thyroid shows a complete response to external beam radiotherapy in 88% of cases, and combined modality treatment with radiotherapy and chemotherapy has resulted in 5-year survival rates of 70% [52–54]. Medullary thyroid cancer also has a more favorable prognosis than UTC, with overall 5-year survival rates of 68–86% [23]. As medullary thyroid cancer can be a manifestation of the familial syndromes of multiple endocrine neoplasia (MEN) type 2A and 2B or familial non-MEN medullary thyroid cancer, its differentiation from UTC may be important in the genetic counseling of siblings and offspring.

Immunohistochemistry is a useful adjunct to histology in this regard and shows a characteristic staining pattern. UTC contains few if any cells that stain positively for thyroglobulin unlike more differentiated forms of thyroid cancer. Stains for keratin and vimentin are positive in up to 80 and 93% of cases, respectively, and confirm an epithelial origin of the tumor [27, 55]. The absence of staining for calcitonin and chromogranin differentiate UTC from medullary thyroid cancer, and the absence of leukocyte markers differentiates UTC from lymphoma [56].

Histological examination of the remnant thyroid tissue adjacent to the tumor reveals associated pathology in many cases. Benign multinodular disease can be identified in the adjacent thyroid remnant in 20% of resected specimens [22]. UTC can be seen in close association with a focus of differentiated papillary or follicular carcinoma in 23–89% of cases, and these lesions are more frequently papillary than follicular in nature [7, 22, 27, 37, 40, 43, 57–59]. The presence of such lesions in close proximity to UTC lends support to the suggestion that many cases of UTC arise by anaplastic transformation from preexisting foci of differentiated thyroid cancer [60]. Further evidence for this lies in the fact that 16–21% of patients with UTC have a prior history of differentiated thyroid cancer [27, 28, 40, 41]. Studies of the genetic material of anaplastic cancer cells and those of the associated differentiated carcinoma show similarities in aneuploidy, candidate gene mutations and chromosomal losses and banding patterns that suggest that transformation has occurred [61–64]. Anaplastic transformation of WDTC to UTC is of clinical importance as it supports an aggressive approach to the surgical resection of thyroid lesions suspicious for malignancy in an attempt to reduce the risk of developing an aggressive cancer within a preexisting low-risk lesion.

The molecular genetics of UTC has been studied to further define the pathogenesis of these cancers. Somatic mutations of the tumor suppressor gene p53 are seen in 32–88% of UTC and yet are uncommon in differentiated thyroid cancer, and this may play a role in the transformation of these tumors as a late step in their dedifferentiation [18, 38, 65–70] Mutations of BRAF, RAS, overexpressed in anaplastic thyroid carcinoma-1 (OEATC-1); bcl-2 and Nm23 genes have also been demonstrated in UTC [18, 61, 67, 71–73]. Expression of B-catenin and E-cadherin, transmembrane glycoproteins involved in intercellular adhesion, is decreased in UTC compared to differentiated cancers [74]. Chromosomal abnormalities are seen with increasing frequency in the progression from differentiated to UTCs, and tissue microarray analysis of a panel of seven genes involved in cell growth signaling showed that a number of genetic mutations are involved in this process [17, 18, 75]. It is likely that a number of sequential gene mutations and genetic events are involved in the pathogenesis of UTC.

Assessment and Evaluation

The presence of a rapidly enlarging neck mass arising from the thyroid confirmed on physical examination should suggest the possibility of UTC, particularly in the elderly. The diagnosis in most cases can be made on FNA biopsy of the neck mass. Careful examination of aspirates by an experienced cytologist can correctly diagnose UTC in 84–90% of cases [76]. The finding of tumor giant cells, marked cellular pleomorphism and atypia, frequent mitoses, and spindle-shaped cells is characteristic [48, 76, 77]. The accuracy of FNA can be limited by the presence of extensive tumor fibrosis, necrosis or hemorrhage, hypocellularity of malignant cells, marked leukocyte infiltration, and the presence

of differing degrees of differentiation within the lesion [76]. Formal surgical biopsy of the thyroid is occasionally required where FNA is not diagnostic.

Imaging has an important role in the evaluation of patients with UTC. Cross-sectional imaging of the neck and mediastinum using computed tomography (CT) can correctly define the extent of invasion into adjacent structures such as the trachea, esophagus, and carotid sheath in a high proportion of cases, and can assess the extent to which invasion or extension of the tumor into the superior mediastinum and its contents has occurred (Fig. 9.5) [78]. UTC are seen as large masses arising from the thyroid, with low attenuation and poorly defined margins on CT. Areas of dense calcification and necrosis are commonly seen within the tumor mass [78]. Magnetic resonance imaging has also been used in the assessment of local invasion with similar accuracy [79]. Correctly defining the extent of extrathyroidal invasion in the neck is invaluable in the preoperative assessment of the surgical resectability of the tumor [78]. Imaging of the chest by CT or plain radiographs should also be performed as a staging investigation, as patients with metastatic disease will have pulmonary lesions in more than 85% of cases (Fig. 9.6) [27, 44]. Positron emission tomography using 18-Fluorodeoxyglucose has also been used to assess the presence and extent of disseminated metastatic disease, and should be considered in the evaluation of UTC [80].

Fiber-optic examination of the larynx and upper airway should be performed to assess vocal cord function and to look for the presence of external invasion of the airway by tumor. Indirect laryngoscopy reveals vocal cord paresis consistent with involvement of the recurrent laryngeal nerve in 25% of cases [37, 38].

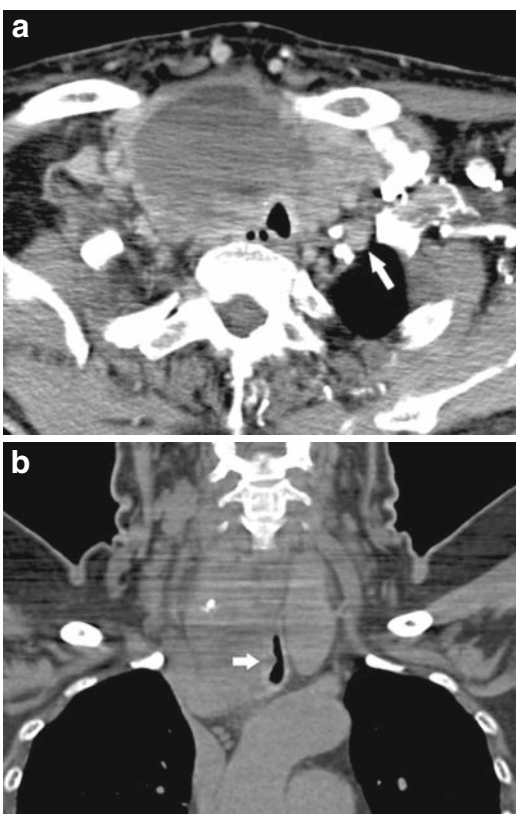

Fig. 9.5. (**A**) Cross-sectional computed tomography appearance of undifferentiated thyroid cancer demonstrating a diffusely invasive large tumor mass arising within the right lobe of the thyroid compressing the airway. Extracapsular invasion involving the adjacent trachea and esophagus and enlarged cervical lymph nodes (*arrow*) are shown. (**B**) Coronal sections demonstrating tumor invasion into the right side of the tracheal wall (*arrow*) by undifferentiated thyroid cancer. A focus of calcification is seen within the tumor.

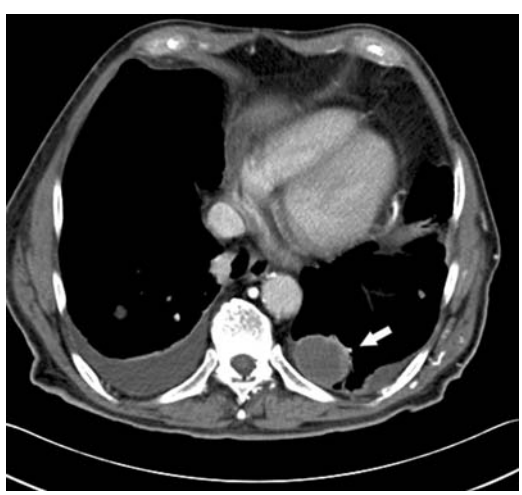

Fig. 9.6. Computed tomography of the thorax of a patient with undifferentiated thyroid cancer demonstrating a 2.5-cm pulmonary metastasis posteriorly within the lower lobe of the left lung (*arrow*). A smaller metastasis within the posterior right lower lobe is also seen.

Management Strategies

The therapeutic options available in the management of UTC include surgical resection and external beam radiotherapy to remove or control local disease within the neck, and systemic therapy with chemotherapy given to enhance the effect of radiotherapy and to control disseminated metastatic disease. UTC presents at an advanced stage with aggressive local invasion or distal metastatic disease present in most patients, and curative resection is possible in only a small proportion [22]. In most cases, the aims of treatment are to control the effects of local tumor growth in the neck, to palliate symptoms of local and disseminated disease, and to improve the quality of life when possible. Modern strategies in managing these malignancies frequently employ a combination of treatment modalities to achieve these aims. Unlike differentiated forms of thyroid cancer, UTC does not take up radioactive iodine, and therefore systemic therapy with this modality is of no clinical benefit. Treatment protocols frequently need to take into consideration the advanced age and poor performance status of many patients with this malignancy.

A review of the therapeutic options available in the management of UTC needs to take into account the different modes of presentation of this disease. UTC tends to present with complications of local growth and invasion (including airway compromise), with complications of disseminated disease, or occasionally as an incidental finding at an early stage. The approach to management must be modified as dictated by the mode of presentation of the patient and the clinical findings after appropriate assessment and investigation.

Clinical Scenario 1: Incidental Finding of UTC

Patients with UTC confined to the thyroid gland represent only 8% of cases, and their prognosis is the most favorable with long-term survival possible after complete resection of the tumor [25]. Many of the cases in this subgroup represent foci of UTC found within larger more differentiated thyroid cancers, or discovered incidentally within the resection specimen at thyroidectomy for another indication [42]. In patients where UTC is found as a small focus without extrathyroidal invasion, a 1-year survival rate of 73% and a 2-year survival rate of 46% have been reported [59]. In this way, although the prognosis of patients with a small focus of UTC completely resected compares favorably to larger clinically apparent anaplastic cancers, additional treatment with external beam radiotherapy and chemotherapy have been recommended due to the risk of recurrent and disseminated disease.

Much of the favorable prognosis associated with small and incidentally found UTC lies in their complete resection prior to progression of disease beyond the thyroid. The majority of patients with UTC unfortunately present with advanced disease where complete resection of the tumor with a curative intent is not possible [22, 27]. Complete surgical resection of UTC confined to the thyroid offers the greatest chance of long-term survival, and has been combined with postoperative chemoradiotherapy to achieve 5-year survival rates of 50–60% [37, 43]. A Japanese study of 11 patients with a small focus of UTC found incidentally, the mortality was 36% and in three patients death was due to complications of locoregional recurrence in the neck [42]. Adjuvant treatment with external beam radiotherapy has been recommended to reduce this risk [28, 42]. In a study of 67 patients with UTC from the Massachusetts Hospital, radiotherapy was given after surgical resection in all cases and was associated with an improvement in survival at higher doses (>45 Gy) [28]. Complete surgical resection was achieved in 18% of cases and was associated with a significantly higher survival than incompletely resected tumors, with 83% of these patients surviving beyond 3 years. Radiotherapy combined with surgical resection has been associated with an improved survival in patients studied in the SEER database [25]. Radiotherapy was, however, not associated with a reduced risk of local recurrence in a large study of 134 patients with UTC from the Mayo Clinic [22]. In this study, surgical resection was performed in 72% of cases, with complete resection achieved in 30%. Most patients received radiotherapy postoperatively. Patients treated surgically had a longer duration of survival than those managed nonoperatively, but no improvement in survival or local recurrence in the neck was seen after complete resection when compared with

incomplete or debulking procedures, with 37% of patients exhibiting local relapse of disease in the neck postoperatively.

Rates of locoregional recurrence within the tumor bed or in cervical lymph nodes are high after surgical resection alone for UTC. UTC has a clear propensity for metastatic dissemination and locoregional recurrence and is not treatable with radioactive iodine, and for these reasons adjuvant treatment with chemotherapy and radiotherapy has been recommended to maximize the chance of achieving local control and to reduce the risk of distant recurrence [27, 37, 39, 43]. Doxorubicin has been the chemotherapy agent most frequently used in this setting, as monotherapy or in combination with cisplatin, and has been associated with acceptable toxicity [37, 43, 81]. In a study of 33 patients at the University of California, San Francisco, complete surgical resection could be performed in eight cases and was followed by adjuvant chemoradiotherapy. The complete resection group had an improved survival compared with incompletely resected or nonresected tumors, with four long-term survivors following complete resection [43]. In a smaller series reported by Tan and coworkers, complete resection of the tumor was achieved in five of 21 patients with UTC and was followed by adjuvant chemoradiotherapy, with three of these patients surviving longer than 2 years [37].

In series that report long-term survival after complete surgical resection of UTC, surviving patients received postoperative radiotherapy and/or chemotherapy in the majority of cases [22, 27, 37, 39, 42, 43, 82]. Given the aggressive behavior of UTC, adjuvant treatment with chemotherapy and radiotherapy is recommended to reduce the risk of recurrent disease following complete resection in patients with small or incidentally found tumors.

Clinical Scenario 2: Extensive Locoregional Disease

Extrathyroidal invasion is present in as many as 82% of UTC, and achieving local control of disease in this setting is difficult [22, 37–39, 41]. In the presence of extensive local invasion of adjacent structures, such as the trachea, esophagus, and major vascular structures, complete surgical resection is not possible and other treatment modalities must be used to obtain control of local tumor growth. Extensive or radical resection of the invaded trachea or esophagus with complex reconstruction is rarely indicated due to the high likelihood of local recurrence in the neck or death from disseminated disease. Progressive airway compromise from unchecked local invasion is highly distressing to the patient and is the mode of death in 15% of cases [44]. The aim of treatment in patients with extensive local disease to achieve local control of tumor growth, for the palliation of symptoms and to extend the duration of life where possible.

Multimodality treatment with chemotherapy and radiotherapy has been used in the setting of advanced local disease to achieve control of tumor growth. Downsizing of tumor volume in the neck may also enable surgical resection in patients who respond to this treatment. One of the first reports of effective treatment for locally advanced UTC was from Memorial Sloane Kettering hospital where radiotherapy was given in combination with doxorubicin for nine patients with UTC, of which only one had complete resection of disease prior to treatment [83]. Complete response to treatment was observed in eight patients, and in six of these responders local control was maintained until death from other causes.

A multimodality treatment protocol developed in Sweden has shown to be effective in the management of locally advanced UTC. The first protocols reported by this group used external beam radiotherapy in combination with bleomycin, 5–fluorouracil, and cyclophosphamide [84]. These chemotherapy agents were replaced with doxorubicin in subsequent protocols [85, 86]. Response to this protocol enabled surgical resection to be subsequently performed in 73% of patients, which was macroscopically complete in 85% of operative cases [86]. Life-threatening complications did not occur, and toxicity did not prevent patients from completing chemoradiotherapy. A reduction in deaths from complications of uncontrolled local tumor invasion was seen with this treatment protocol, occurring in only 24% of cases [84, 86]. Local recurrence was seen in only 40% of cases, and in only 18% of patients where surgical resection was performed. This strategy was effective in controlling the effects of local tumor growth, but survival was limited by the onset of disseminated disease. Mean

survival durations of 2–4.5 months were reported in the groups studied, with an overall 1 year survival rate of only 16%. However, long-term survival (>2 years) was seen in 10% of patients [84].

Results of multimodality therapy from other centers confirm a role for this strategy in the management of locally advanced UTC. In a report of 30 patients with UTC from a French group, of which extrathyroidal invasion was present in 26, chemotherapy with doxorubicin and cisplatin was combined with radiotherapy and given prior to surgical resection or postoperatively [82]. In seven patients with unresectable disease at presentation, tumor response to therapy enabled subsequent complete resection in three cases. In total, surgical resection was performed in 24 cases and was macroscopically complete in 12. Complete surgical resection was associated with a significant survival advantage in this setting. A complete local response to therapy was found in 63% of patients. Overall 3-year survival was 27% (median survival 10 months), with 68% of deaths due to complications of metastatic disease and only 5% due to locoregional failure. Seven patients remained disease free at follow up (3-year disease-free survival rate 24%). There was, however, a high rate of toxicity in this study from neutropenia and bone marrow suppression (seen in 70%), limiting its role in the management of frail or elderly patients.

Newer chemotherapy agents for the systemic treatment of UTC have been studied and associated with better results from treatment than standard regimes. A phase 2 trial of paclitaxel has been reported which has shown the effectiveness of this agent [87]. In this trial of 20 patients with locally advanced or metastatic UTC (including 42% who had previously undergone surgical resection), response to therapy was observed in 53% of patients and was complete in one patient only. The treatment protocol was well tolerated and associated with an acceptable risk profile. The addition of taxol-based chemotherapy to multimodality treatment protocols may improve the long-term results of treatment for UTC.

For patients with extensive locoregional disease, combination chemotherapy and radiotherapy can be effective in controlling local complications. In patients who respond to a trial of chemoradiotherapy, a sufficient downsizing of disease in the neck may enable subsequent surgical resection of disease to be performed.

Clinical Scenario 3: Distant Metastatic Disease

Disseminated metastatic disease is present in 43–64% of patients with UTC at the time of first assessment [22, 25, 27, 28, 38, 43]. Where disseminated disease is present, prognosis is extremely poor with very few patients surviving for more than 12 months [22, 25]. Systemic therapy for metastatic disease has a very limited role in the management of metastatic UTC, and the results after treatment with existing chemotherapy regimes remain disappointing [88]. In a report of nine patients undergoing chemotherapy with doxorubicin and bleomycin for metastatic UTC at the University of Padova, clinical response was seen in only a single patient and the group had a median survival of only 5.7 months [89]. A larger study of chemotherapy for advanced thyroid cancer including 39 patients with UTC comparing monotherapy with doxorubicin with combination therapy with doxorubicin and cisplatin showed a clinical response in 26% of patients receiving the combined treatment, of which half displayed a complete response [90]. Significantly more patients had a complete response to treatment after combination chemotherapy in this study. Combination therapy was however associated with considerable toxicity, causing life-threatening complications in 12% of patients. Chemotherapy with newer agents such as paclitaxel has been associated with improvements in clinical response with lower rates of toxicity. In the phase 2 trial of paclitaxel for locally advanced and metastatic UTC, few patients had toxicities more severe than grade 2, and no life-threatening complications were reported [87]. Fifty-three percent of patients exhibited a clinical response to paclitaxel and had a mean duration of survival of 32 weeks, compared with 10 weeks for nonresponders, although this difference was not statistically significant.

In patients with UTC where distant metastases are present, complications of disseminated disease will be the determinant of survival in most cases, and aggressive multimodality treatment with chemoradiotherapy and surgical resection will in most cases not influence

survival. An exception to this may be where extensive local disease is also present and where external beam radiotherapy and chemotherapy can be given for local control of the tumor mass with palliative intent [84, 86]. The distress of progressive airway compromise and other local complications are considerable, and chemoradiotherapy for local control has been recommended in the setting of disseminated metastatic disease for this reason [84, 86]. Radiotherapy also has a role in the palliation of metastatic disease and can be directed to sites of skeletal or brain metastases for control of local symptoms [91].

Scenario 4: Acute Airway Compromise

Invasion of the larynx or trachea is present in up to 50% of UTC at the time of presentation, and less commonly (18% of cases) UTC can present with symptoms of acute airway obstruction necessitating urgent intervention [38, 39]. In many of these cases, endotracheal intubation is performed as an emergency procedure to achieve control of the airway, allowing subsequent clinical evaluation of the obstructing mass with appropriate imaging and diagnostic pathology. CT imaging of the neck and mediastinum can assess the extent of local invasion into the airway and other adjacent vital structures, and can be used to assess the feasibility of surgical debulking or resection in relieving the obstruction (Fig. 9.7). Metastatic disease to mediastinal lymph nodes or the lungs may also be seen. Flexible bronchoscopy and esophagoscopy should be performed to assess whether invasion into the lumen of the airway or esophagus has occurred and can be used to obtain biopsy material of the tumor if this is present. FNA biopsy should be performed to confirm UTC and rule out other thyroid malignancies which may be more responsive to treatment. More definitive control of the airway can be achieved by surgical intervention or by the insertion of a tracheal stent. Surgical options for the relief of airway obstruction consist of surgical resection, division of the isthmus, tumor debulking, or by the formation of tracheostomy. Complete surgical resection of UTC is rarely possible in the setting of acute airway obstruction due to the advanced nature of local invasion. Tracheostomy has been performed in 7–33% of patients with UTC in published series and can be technically difficult due the extent and bulk of local disease [37, 38]. In a study of 69 patients who underwent tracheostomy in the setting of locally advanced thyroid cancer, patients with UTC had a survival rate of only 25% at 3 months [92]. Survival was worse for patients with UTC after tracheostomy compared with those who did not undergo this procedure, although this probably represented the selection of more aggressive and advanced malignancies. More recently, the insertion of self-expanding stents under bronchoscopic control to traverse the region of obstruction has

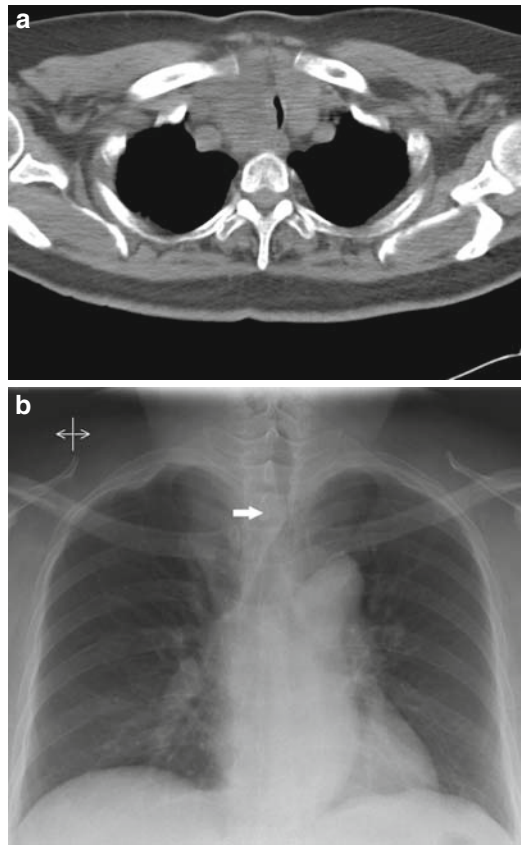

Fig. 9.7. (**A**) Cross-sectional computed tomography appearance of undifferentiated thyroid cancer arising within a long-standing multinodular goiter in a 58-year-old female. The patient presented with acute airway compromise and distress. Invasion and compression of the trachea and esophagus are demonstrated. (**B**) Chest radiograph of the patient showing compression and deviation of the trachea (*arrow*).

been performed for longer-term airway control [93–95]. This technique can be combined with balloon dilation of the narrowed segment and laser ablation of invasive intraluminal disease, and has been successful in achieving airway control in 92% of patients with obstruction from thyroid malignancy [95]. Potential complications of this technique include stent migration, stent obstruction, and in-growth of tumor into the stent causing recurrent obstruction [95].

Outcomes and Prognosis

Despite improvements in diagnosis, surgical technique and the development of newer multimodal chemotherapy and radiation therapy protocols, the prognosis of patients with UTC remains poor (Table 9.1). Complications of disseminated metastatic disease are frequently the cause of death and limit survival even where effective local control can be achieved with aggressive surgical resection and radiotherapy. The majority of patients with UTC will die from complications of disseminated metastatic disease (usually pulmonary) or invasion of vital structures within the neck [44]. Airway obstruction due to tumor invasion is the cause of death in 16–50% of cases [37, 44].

studies, with median survival durations of 3–7 months, and only a small proportion of patients surviving for longer than 1 year [27, 28, 37–39, 43]. A survival analysis of 516 cases of UTC from the SEER database found a disease-specific mortality of 80.7% at 12 months, with patient age less than 60 years, tumor confined to the thyroid and surgical resection of the tumor combined with radiotherapy being associated with a greater probability of survival on multivariate analysis [25]. Studies involving smaller series of patients with UTC have found that younger age at presentation, smaller tumor size (<5–6 cm), the absence of disseminated metastatic disease, and complete surgical removal of the tumor have all been associated with an improved probability of survival or longer survival duration [22, 27, 28, 37–39, 43]. Where complete macroscopic resection of the tumor can be performed, aggressive multimodality treatment with surgery followed by chemoradiotherapy has been associated with long-term survival in a small proportion of selected patients [43]. Many of the longer-term survivors reported in case series of UTC are patients with small foci of anaplastic carcinoma seen within larger well-differentiated tumors or where UTC is found incidentally at thyroidectomy [28, 40–42]. Such patients represent a small but distinct subgroup of UTC associated with a more favorable prognosis.

Table 9.1. Outcomes after treatment for undifferentiated thyroid carcinoma

Author	Year	Patients	Surgical resection (%)	Survival (%)	Mean survival (months)
McIvor [22]	1949–1999	134	72	9.7% – 1 year	3
Venkatesh [27]	1950–1987	121	73	14% – 2 year	7.2
Nilsson [84]	1971–1997	81	52	10% – 2 year	2.5–5.4
Pierie [28]	1969–1999	67	67	16% – 3 year	ND
Sugitani [39]	1976–1999	44	59	16% – 1 year	6
Sugino [42]	1989–1999	40	65	20% – 2 year	ND
Lo [38]	1968–1997	38	47	4% – 2 year	1.3
Haigh [43]	1973–1998	33	79	20% – 2 year	3.8
De Crevoisier [82]	1990–2000	30	80	27% – 3 year	10
Tan [37]	1968–1992	22	81	14% – 2 year	4.5

ND – not described

The 134 patients with UTC managed in a 50-year period at the Mayo Clinic had a median survival of only 3 months with only 9.7% of patients surviving beyond 1 year [22]. Similar outcomes have been documented in other

The development of metastatic disease is most frequently the determinant of survival in patients with UTC, and research into novel systemic therapies has been undertaken in an effort to improve the dismal outlook for patients with

disseminated disease. Targeted molecular therapy with the proteosome inhibitor bortezomib and the selective tyrosine kinase inhibitor imatinib mesylate have shown activity against UTC in vitro [96, 97]. Adenovirus-mediated gene therapy targeting the p53 gene mutation has also been attempted [98]. Redifferentiation of UTC cells to promote the uptake of radioactive iodine has also been examined experimentally, using reverse transcriptase inhibitors and virus-mediated thyroid transcription factor-1 gene transfer [99, 100]. Until such time as effective systemic therapies are discovered, multimodality therapy with chemotherapy and radiotherapy followed by complete surgical resection when possible offers the greatest chance of achieving local control, palliation, and extension of survival in patients with this highly aggressive malignancy.

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10

Postoperative Management of Well-Differentiated Thyroid Cancer

R. Michael Tuttle and Rebecca Leboeuf

Introduction

For the nonsurgeon, postoperative management of thyroid cancer usually begins a few days or weeks after surgery when the patient returns to the office to discuss the final pathology report and determine if any additional therapy is necessary. Depending on the specifics of the individual case, additional therapies that may be required can include further surgery, radioactive iodine ablation, thyroid-stimulating hormone (TSH) suppression with levothyroxine, external beam irradiation, or other systemic therapies.

The decision to recommend additional treatments beyond the initial thyroid surgery should be based on an accurate assessment of risk of recurrence and death from thyroid cancer for each individual patient. Recently, several international authorities on thyroid cancer have published guidelines in which estimates of risk of recurrence and risk of disease-specific death are used to guide both initial treatment and follow-up recommendations [1–5].

In this chapter, we will review a practical approach to risk stratification for well-differentiated thyroid cancer that can be used to estimate both the risk of recurrence and the risk of death from thyroid cancer. By balancing the risk and benefits of additional therapies with this understanding of the likely clinical course, a rationale treatment and follow-up plan can be developed for individual patients.

Initial Risk Stratification

Over the years, several staging systems have been published that can accurately identify patients at either low or high risk of dying from thyroid cancer [6–13]. These staging systems predict disease-specific mortality based on clinical data that can be considered either as patient-related factors (age and gender) or tumor-related factors (size of primary, histology, gross extrathyroidal extension, completeness of resection, cervical lymph node involvement, or distant metastasis) [14]. From a simplified clinical perspective, these important clinical factors can be used to stratify the risk of dying from thyroid cancer into very low, low, intermediate, and high (see Table 10.1) [15, 16].

In thyroid cancer, the risk of recurrence does not always parallel the risk of disease-specific death [17]. This is particularly apparent in the young thyroid cancer patients where the risk of recurrence is very high, but the risk of death is very low. Therefore, in addition to determining the risk of disease-specific death in thyroid cancer patients, it is also necessary to separately estimate the risk of recurrence. In many cases, additional treatments may be effective at decreasing recurrence, but have little impact on overall survival, especially in young patients who are at high risk of recurrence but very low risk of death from thyroid cancer [2, 14].

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Table 10.1. Risk of death from thyroid cancer

	Very low risk	Low risk	Intermediate risk	High risk
Age at diagnosis	<45 years	<45 years	Young patients (<45 years) • Classic PTC > 4 cm • Or vascular invasion • Or extrathyroidal extension • Or worrisome histology of any size**	>45 years
Primary tumor size	<1 cm	1–4 cm	Older patients (>45 years) • Classic PTC < 4 cm • Or extrathyroidal extension • Or worrisome histology < 1–2 cm confined to the thyroid**	>4 cm classic PTC
Histology	Classic PTC, confined to the thyroid gland*	Classic PTC, confined to the thyroid gland*	Histology in conjunction with age as above	Worrisome histology >1–2 cm**
Completeness of resection	Complete resection	Complete resection	Complete resection	Incomplete tumor resection
Lymph node involvement	None apparent	Present or absent***	Present or absent***	Present or absent***
Distant metastasis	None apparent	None apparent	None apparent	Present

*Confined to the thyroid gland (even if multifocal) with no evidence of vascular invasion or extrathyroidal extension

**Worrisome histologies includes histologic subtypes of papillary thyroid cancer such as tall cell variant, columnar variant, insular variant, and poorly differentiated thyroid cancers.

***Cervical LN metastases in older patients, but probably not in younger patients, may confer an increased risk of death from disease.

Only those patients meeting all criteria within the respective column would be classified as very low risk or low risk. Older patients with either incomplete tumor resection or presence of distant metastasis are considered high risk irrespective of tumor size and specific histology. Patients with a combination of risk factors (age, histology, and tumor size) crossing over between columns are classified as intermediate-risk patients.

Table 10.2. Risk stratification for the likelihood of clinically evident thyroid cancer recurrence following complete resection of primary tumor in patients with no evidence of distant metastases at initial evaluation

	Low risk	Intermediate risk	High risk
Age at diagnosis	Any age	20–60 years	<20 or >60 years
Primary tumor size	<1 cm	1–4 cm	>4 cm
Histology	Classic PTC, confined to the thyroid gland	Classic PTC, minor extrathyroidal extension, or vascular invasion, or multifocal disease	Other than classic PTC, gross extrathyroidal extension or vascular invasion
Lymph node involvement	None apparent	Present or absent	Present

Patients with incomplete tumor resection or distant metastasis at diagnosis are very likely to have persistent disease even after aggressive initial therapy and therefore are dealt with differently than the more usual patient without evidence of distant metastasis in which all gross evidence of disease has been resected and are therefore not included in this risk stratification scheme.

Based on many of the same clinical and pathological characteristics that are used in the staging systems that predict death from thyroid cancer, the risk of recurrence can be estimated in an individual patient to be either low, intermediate, or high (see Table 10.2) [15, 16]. To be conservative, patients with a histology more worrisome than classic papillary thyroid cancer (PTC), microscopic multifocal disease, or microscopic extrathyroidal extension are considered to be at intermediate risk. Additional research is needed to make sure that we are not unnecessarily upstaging these patients, particularly when the primary tumor is quite small.

Patients with incomplete tumor resection or known distant metastases at presentation almost always require additional therapy [2, 18, 19]. They require individualized therapy and careful assessment of response to therapy evaluations to guide their management.

Table 10.3. Data necessary for accurate risk stratification

Preoperative findings	Physical examination
	Vocal cord function
	Cross-sectional imaging (if obtained)
Intraoperative findings	Extent of thyroid surgery
	Extent of lymph node dissection
	Presence of gross extrathyroidal extension
	Involvement of major structures in the neck
	Completeness of tumor resection
Pathology findings	Histopathology
	Molecular characterization
Laboratory findings	Serum thyroglobulin
	Calcium, albumin, PTH
	TSH, Free T4

Initial Postoperative Visit

Accurate risk stratification begins with a careful analysis of all the available clinical data that have been obtained for that individual patient. At this initial postoperative visit, all data obtained during the preoperative evaluation, the intraoperative procedure, as well as the postoperative pathology report and lab data are analyzed in an attempt to understand both the extent of disease and likely clinical course so that we can tailor specific treatment recommendations for an individual patient (see Table 10.3).

It is important to emphasize that the thyroid pathology report does not provide all the data necessary for accurate risk stratification. In order to properly risk stratify patients, it is critical that treating clinicians have a very good understanding of the preoperative, intraoperative, and postoperative findings in order to gain a full appreciation of the extent and potential aggressiveness of an individual patient's thyroid cancer. Unfortunately, patients are often classified as either low or high risk based on the pathology report alone without incorporating all other available clinical information into the risk stratification scheme. This can result in either an overestimate or underestimate of the risk for death or recurrence.

For example, a 35-year-old female patient with a 1.5-cm papillary thyroid cancer could be inappropriately classified as having a low risk for disease-specific death and recurrence if the "extrathyroidal extension" described on the pathology report was mistakenly assumed to reflect minimal microscopic extracapsular extension rather that the margin of extrathyroidal gross tumor invading into major neck structures. Similarly, even in the setting of a very small papillary or follicular thyroid cancer, the presence of pulmonary nodules on a preoperative chest radiograph or a postoperative serum thyroglobulin (Tg) of 1,500 ng/mL would raise the suspicion of distant metastases and likely lead to additional diagnostic evaluations and therapies.

While most patients have a neck ultrasound and chest radiograph prior to surgery, additional use of cross-sectional imaging studies is not routinely recommended unless the patient is at an increased risk for distant metastases [2, 3]. Since patients classified as high risk for recurrence or death are also often at significant risk for distant metastases, cross-sectional imaging of the lungs and brain is recommended to identify other sites of disease that may need therapy or close observation. Likewise, aggressive histologies such as Hurthle cell carcinoma, tall cell or poorly differentiated variants of papillary thyroid may concentrate radioactive iodine (RAI) poorly and therefore are often better detected with 18 FDG PET scanning than RAI scanning [2, 14, 20]. It is important to avoid intravenous contrast

containing iodine in patient that are likely to require RAI since the large amount of stable iodine present in CT contrast will render RAI ineffective for at least 2–3 months.

In many cases, the adequacy of surgical resection cannot be determined by the pathology report alone. For example, a pathology report that notes "positive margins" or "extrathyroidal extension" could reflect either (a) minor extension into perithyroidal adipose tissue, or minor invasion into strap muscles that was completely resected, or (b) the surgical margin of gross disease that was not completely resectable. Clearly, the risk stratification and subsequent therapeutic recommendations in these two situations could vary markedly.

Therefore, it is critical that the intraoperative findings be transmitted to the endocrinologists/nuclear medicine physicians in a format that is easily understandable to the nonsurgeon. Unfortunately, while the dictated operative reports contain the details of the surgical procedure, often in excruciating detail, they are difficult for nonsurgeons to decipher and understand. Therefore, either (a) direct communication, or (b) an operative note with a section clearly marked as "intraoperative findings," or (c) a separate note (or diagram) succinctly explaining the surgical procedure and intraoperative findings will dramatically improve the endocrinologists understanding of the intraoperative findings.

Once the endocrinologist has a thorough understanding of the preoperative and intraoperative findings, a careful review of the pathology description will provide invaluable information that can be used to further guide risk stratification and treatment recommendations. While the size of the primary tumor is the major determinant of clinical outcome, the presence of vascular invasion, extrathyroidal (or extranodal) extension, lymphatic involvement, and worrisome histological subtypes of thyroid cancer (such as tall cell variants, columnar variants, insular variants, and poorly differentiated subtypes) may also be associated with an increased risk of recurrence and/or death. Therefore, regardless of size of the primary, these additional worrisome features will increase our estimate for risk of recurrence and risk of death and often lead to more aggressive additional therapies.

Over the last several years, our understanding of the molecular biology of thyroid cancer has increased dramatically [21]. Several authors have suggested that the presence of specific molecular abnormalities can provide important information as to the risk of recurrence [22–24]. For example, it has recently been demonstrated that tumors harboring BRAF mutations appear to display a more aggressive clinical course [25, 26]. Since, many pathology departments now offer molecular analysis of malignancies, it is likely that molecular profiling will be added to our risk stratification schemes in the years to come.

In our practice, we use a serum Tg measurement, about 10 days after thyroidectomy, to guide our risk stratification. This is particularly important in low-risk patients that we are considering following with observation alone without RAI ablation. While the precise cutoff values for "normal post-op" Tg are not well defined, we generally consider a serum Tg value less than 10 ng/mL (with a TSH of about 1–2 mIU/mL) about 10 days after surgery to be consistent with normal remnant thyroid. Usually, the Tg continues to decline over several weeks such that by 4–6 weeks postoperatively the serum Tg (with mild TSH suppression) is less than 3–5 ng/mL and often less than 1 ng/mL. Therefore, if the serum Tg is elevated at the 10-day visit, a repeat value is obtained 4 weeks later to obtain a nadir postoperative value. Serum Tg levels that remain above these arbitrary cutoff values about 1 month after total thyroidectomy would raise the suspicion for persistent disease and lead to additional cross-sectional and nuclear medicine imaging.

Goals of Initial Therapy

The goals of initial therapy are to surgically remove or destroy all thyroid cancer cells while minimizing treatment and disease-related morbidity [2]. Our initial therapies, if successful, should result in a decrease in both local and distant recurrence as well as disease-specific mortality. Because every treatment has potential risk and side effects, it is imperative that the risks associated with our treatment recommendations are justified by the risk of recurrence or disease-specific death.

Extent of Initial Thyroid Surgery

Most of the published guidelines recommend total thyroidectomy as the procedure of choice in patients with biopsy-proven papillary thyroid cancer [14]. In most large series, a total thyroidectomy is associated with lower recurrence rates than unilateral thyroid surgeries [10, 17, 27]. However, a unilateral lobectomy achieves the same excellent disease-specific survival rates in patients at very low or low risk of dying from thyroid cancer (see Table 10.1) [28]. With careful follow up (primarily neck ultrasonography), the few recurrences that develop years later in low-risk patients initially treated with less than total thyroidectomy are usually readily detectable and easily treated with additional surgery with or without postoperative RAI. Therefore, less than total thyroidectomy is still considered an acceptable surgical option for patients at low risk of dying from thyroid cancer.

However, for patients at intermediate or high risk of either (a) dying from thyroid cancer (see Table 10.1) or (b) having a clinically evident recurrence (see Table 10.2), we routinely recommend total thyroidectomy. In most series, bilateral thyroid surgery in high-risk patients has been shown to have a beneficial effect on both disease-specific survival and risk of recurrence[2, 14]. Additionally, since radioactive iodine ablation is routinely used in these high-risk patients, a total thyroidectomy is required as initial management.

Very often small papillary thyroid cancers (<1 cm) are detected after lobectomy for predominantly benign thyroid disease. These tumors are at very low risk of disease-specific death (<1%) and low risk for having cervical or distant metastases (less than 2–3%). Two recent publications have detailed the controversies embodied in the management of these low-risk patients [29, 30]. In our opinion, in the absence of other evidence of disease in the contralateral lobe (multifocal disease), neck lymph nodes or distant sites, patients with classic primary papillary thyroid cancers less than 1 cm detected at the time of lobectomy for predominantly benign disease can be followed with observation without the need for a completion thyroidectomy or RAI ablation. Obviously, the development of suspicious lesions in the contralateral lobe or cervical lymph nodes would prompt additional evaluations and likely completion thyroidectomy.

The most controversial patients are those with well-differentiated thyroid cancers, confined to the thyroid, that are between 1 and 4 cm in size. By nearly all staging systems, these patients are at low risk for death from thyroid cancer but are variously classified as either low or intermediate risk for recurrence. In many centers, the endocrinologists want to give RAI ablation to these intermediate-risk patients, and therefore completion thyroidectomy is mandated. However, in our center, if the primary tumor is less than 3–4 cm, confined to the thyroid without worrisome histologic features, the contralateral lobe is normal on ultrasound without evidence of lymph node involvement, and the serum Tg is in the expected postoperative range, we do not feel that additional surgery or RAI ablation will improve disease-specific survival and therefore do not routinely recommend either radioactive iodine ablation (if total thyroidectomy was done) or a completion thyroidectomy (if a unilateral surgical procedure was done). However, since this an area of continued controversy, we do discuss in great detail the risk and benefits of a completion thyroidectomy with or without RAI ablation in these patients at intermediate risk for recurrence. That being said, most of our intermediate-risk patients chose to follow without additional surgery or RAI ablation unless abnormalities are subsequently detected on follow-up neck ultrasonography or serum Tg levels.

In some cases, the final pathology report results in upstaging a patient initially thought to be low risk based on preoperatively and intraoperative findings. If this is the case, then a completion thyroidectomy is recommended. For example, a patient with a 1.5-cm tumor that was tentatively staged as low risk prior to and during surgery may require a subsequent completion thyroidectomy if on final pathology worrisome histologic features (e.g., microscopic vascular invasion, worrisome histologic subtype, and microscopic extrathyroidal extension) are detected. Because the final pathology report is required for an accurate final risk assessment, many argue for a total thyroidectomy in all patients with a preoperative diagnosis of well-differentiated thyroid cancer. While this is

not an unreasonable approach, it will subject many low-risk patients to the risks of a bilateral thyroid surgical procedure while achieving little, if any, survival benefit.

Very often the extent of initial surgery is influenced by the follow-up methods and paradigms that will be used by the referring endocrinologists. If RAI ablation is planned, then total thyroidectomy is required to minimize the volume of normal thyroid tissue that would preferentially concentrate the RAI and prevent detection/therapy of metastatic lesions. Total thyroidectomy and RAI ablation has the additional benefit of resulting in serum Tg levels that are either very low or undetectable. The maximum sensitivity and specificity of serum Tg is achieved when all normal thyroid tissue has been destroyed (total thyroidectomy and RAI ablation). While not required for follow up in patients at low to in termediate risk for recurrence, many endocrinologists are much more comfortable following thyroid cancer patients previously treated with total thyroidectomy and RAI ablation. As such, they will often prefer total thyroidectomy and RAI ablation in nearly all but the very low-risk patients.

From a practical standpoint, it appears that the wide spread use of neck ultrasonography has resulted in fewer unilateral thyroid procedures and more total thyroidectomy procedures even in low-risk patients. It is hard to imagine doing less than a total thyroidectomy with biopsy-proven papillary thyroid cancer if structural abnormalities are present in the contralateral lobe (even though the vast majority of these abnormalities will be benign). Furthermore, follow-up ultrasonography commonly detects abnormalities in the contralateral lobe that is likely part of the normal aging process of the thyroid or subsequent development of benign thyroid disease that is common as patient's age, but that will be, nonetheless, worrisome to both the patient and the treating physician. Based on these practical follow-up issues and a potential benefit of decreased recurrence, many low-risk patients opt for a total thyroidectomy as their initial surgical procedure even though this approach provides no substantial survival benefit and probably increases the risk of operative complications (hypoparathyroidism, injury to recurrent laryngeal nerve).

Radioactive Iodine Remnant Ablation

The use of RAI in the post-thyroidectomy setting to destroy the microscopic residual thyroid bed tissue has become know as RAI remnant ablation (RRA). Because RRA has been shown to decrease recurrence rates and disease-specific mortality rates in high-risk patients, it must also have a tumoricidal effect on thyroid cancer deposits. While all of the published guidelines support the routine use of RRA in patients at moderate to high risk of recurrence or death, there continues to be considerable controversy over RRA in low-risk patients [14].

While the final decision regarding RAI ablation is made during a careful discussion of the risks and benefits with an individual patient, in general we would recommend RAI ablation in patients at intermediate to high risk of dying from thyroid cancer (Table 10.1) or high risk of recurrence (Table 10.2). We see little clinical benefit in routine use of RAI ablation in patients at very low risk of dying from thyroid cancer or at low risk of recurrence.

In high-risk patients, RRA probably reduces recurrence and improves overall survival. However, it is unlikely that RRA will improve the already excellent survival of low-risk patients. Likewise, data on decreasing recurrence rates in low-risk patients is much less convincing. Therefore, the potential benefits of RAI in low-risk patients probably has more to do with an increased sensitivity for detection of recurrent disease with RAI scanning and serum Tg measurements than it does for a true survival or recurrence benefit. However, without a documented survival benefit, it is hard to justify the routine use of RAI in low-risk patients.

The few recurrences that develop in this low-risk group of patients are usually readily detectable on follow-up ultrasonography or a rising serum Tg. Unlike 30 years ago when the primary method for detection of recurrent disease was physical examination, routine use of neck ultrasonography and serum Tg measurements during follow up should identify the few recurrences that develop in these low-risk patients at an early stage in which they can be easily treated with additional surgery or radioactive iodine.

Fortunately, RAI is a very safe targeted therapy that has been used since the late 1940s in the treatment of thyroid cancer. Following an initial ablative administered activity of 75–100 mCi, many patients will develop temporary alterations in taste that last for about a month, or salivary gland swelling/tenderness that may last for a few months. Unfortunately, 1–2% will develop persistent salivary gland swelling and pain, often with dry mouth which can lead to difficulty in swallowing, persistent taste alterations, gum disease, and dental cavities. Second malignancies, such as leukemia, are associated with multiple doses over time and are not associated with the usual dose of RAI given as initial RRA. The rate of permanent side effects increases with increasing administered activity both as single doses and cumulative doses over time.

In the past, RRA required a prolonged period (4–6 weeks) of thyroid hormone withdrawal to elevate the TSH to more than 30–40 mIU/mL so that the RAI would be adequately concentrated by both the normal thyroid tissue and malignant thyroid cells [14]. In late 2007, recombinant human TSH (Thyrogen, Genzyme) was approved by the US Food and Drug Administration as an adjunct to RRA. From a practical standpoint, patients can be discharged on levothyroxine after total thyroidectomy with the goal of achieving appropriate TSH suppression (discussed below). The patient remains on levothyroxine suppression during RRA, and recombinant human TSH (two injections of 0.9 mg on two consecutive days) is used to raise the TSH to levels sufficient to stimulate the uptake of RAI into normal and malignant thyroid cells. In our center, a tracer dose of ^{123}I is administered immediately after the second rhTSH injection. A pretherapy whole-body scan is performed the following day after which the ablation dose of ^{131}I is given to the patient. This approach avoids the marked hypothyroid symptoms associated with thyroid hormone withdrawal that used to be a necessary part of RRA.

In addition to an elevated TSH, the uptake of RAI into thyroid cells is also maximized by the patient following a low-iodine diet. Most nuclear medicine groups recommend a low-iodine diet for 1–2 weeks prior to RRA in order to deplete the body stores of iodine [14]. In this way, the relatively small amounts of RAI given are preferentially concentrated by the thyroid cells (rather than the stable, nonradioactive iodine present in our foods). It is for this reason that it is important to avoid iodinated contrast materials in patients likely to need RRA. The huge load of iodine contained in these iodinated contrast materials take several months to be excreted from the body and will markedly diminish the diagnostic and therapeutic utility of RAI for several months.

TSH Suppression

TSH suppression with supraphysiologic doses of levothyroxine has been a cornerstone of thyroid cancer therapy for more than 40 years [31, 32]. However, over the last 10–15 years, an increased appreciation of the risk of atrial fibrillation and osteoporosis associated with mild hyperthyroidism has led to a more critical analysis of the degree of thyroid hormone suppression that is necessary based on the risk stratification of the patient.

Several studies now suggest that aggressive TSH suppression (less than 0.1 mIU/mL) may be beneficial in high-risk patients but the data in low- to intermediate-risk patients are less convincing [33, 34]. Therefore, while we routinely recommend aggressive TSH suppression in high-risk patients, the goal TSH for most other thyroid cancer patients ranges from 0.1 to 0.4 mIU/mL [2, 5]. However, we are much less aggressive in patients at low or very low risk for recurrence or death allowing the TSH to range from 0.5 to 1.5 mIU/mL. This approach balances the risk of recurrence and death with the risks of therapy and should provide adequate suppression based on the individual patient risk. During follow up, the degree of TSH suppression is re-evaluated every few years to make sure the goal TSH continues to correlate with the risk of recurrence and death.

External Beam Irradiation

Fortunately, external beam radiotherapy (EBRT) is seldom necessary as part of the initial therapy of papillary thyroid cancer [18, 35]. However, EBRT does have a very well-defined role in patients who present with inoperable disease or

gross disease remaining after attempted surgical removal. Usually, these are older patients with RAI refractory, poorly differentiated histologies.

In addition, EBRT probably has a role in older patients presenting with gross extrathyroidal extension, in which, even though all the evidence of gross disease was removed, they have persistent microscopic or low-volume disease that is unlikely to respond to RAI therapy [36]. We will often use postoperative 18 FDG PET scanning in conjunction with diagnostic RAI scanning to identify patients with FGD PET-positive, RAI-negative residual disease that are at high risk of local recurrence. In these patients, the risk of RAI refractory recurrence outweighs the risks and side effects of EBRT therapy.

Outside the neck, EBRT is a useful tool to treat macroscopic disease that is unlikely to respond to RAI treatment [35]. These are often bone metastases in which EBRT is remarkably effective in palliating pain and preventing disease progression that could result in structural instability of the bone. EBRT is also a useful tool in treating brain metastases that cannot be safely resected.

Systemic Therapy for Distant Metastases

Although distant metastases are present at initial presentation in less than 5% of patients with papillary thyroid cancer, they can be identified in long-term follow up in as many as 10% of patients with papillary thyroid cancer and 20% of patients with follicular thyroid cancer [2]. In essentially all cases, RAI is the initial attempted therapy. Fortunately, this is a quite effective therapy for small-volume, well-differentiated thyroid cancer. Unfortunately, it is much less effective in treating large-volume, well-differentiated thyroid cancer even if the metastatic disease concentrates RAI. Recently, 18 FDG PET scanning has emerged as a powerful tool to predict disease progression, responsiveness to RAI, and even disease-specific mortality [20]. In general, metastatic lesions that are markedly positive on FDG PET scanning are not-RAI avid and do not respond to even very high dose RAI therapy [37].

Many patients have distant metastases detectable by cross-sectional imaging that are slow growing (usually FDG PET negative) in which the risks of systemic therapy probably outweigh the potential benefit. However, patients with distant metastasis that are structurally progressive (usually FDG PET positive) have a life-threatening disease that warrants strong consideration for systemic therapy. Unfortunately, the traditional chemotherapy regimens used (platinum or adriamycin based) have been very disappointing with meaningful, durable response rates of less than 10–15%.

Over the past 5 years, a renewed interest in clinical trials in thyroid cancer has resulted in several phase 2 trials, specific to thyroid cancer, being opened both in the USA and abroad [19]. Many of these trials are using targeted therapy to inhibit key steps in the receptor tyrosine kinase pathways such as vascular endothelial growth factor receptor, RET, and BRAF. Both the American Thyroid Association (http://www.thyroidtrials.org/) and the National Cancer Institute (http://www.cancer.gov/clinicaltrials/search) maintain a list of currently available clinical trials on their respective websites. Eligibility for most of these trials is usually structurally progressive disease with a minimum target lesion size of about 1 cm that is RAI refractory and not amenable to surgical resection.

Strategy for Detecting Persistent/Recurrent Disease

Just as risk stratification informed our initial therapeutic choices, so should it guide our follow-up management paradigm [15, 16]. Disease detection tools should be selected based on the risk of recurrence and likely sites of recurrence. Clearly, the most likely site of recurrence in well-differentiated thyroid cancer patients is the neck: either in the thyroid bed, in cervical lymph nodes, or soft tissue at the site of initial surgical removal. Therefore, it is not surprising that neck ultrasonography has gained increasing popularity as our primary tool for detection of recurrent disease.

Similarly, serum Tg has become our main tool for detecting the presence of persistent or recurrent disease in the neck or elsewhere in the body [38]. Most recurrences are heralded by a rise in serum Tg either on suppression or after stimulation. However, serum Tg will often miss very small-volume cervical lymph node metastases and may be less reliable in poorly

differentiated thyroid cancers that tend to make Tg more poorly. In addition, serum Tg determinations are not reliable in the presence of anti-Tg antibodies that are present in 20–25% of thyroid cancer patients [39]. Often the anti-Tg antibodies interfere with the Tg assay, usually resulting in a false lowering of the Tg value. To complicate matters further, serum Tg values vary dramatically (as much as 5–10 ng/mL) when the same blood sample is run in different commercial assays [40]. Therefore, in order to obtain maximal sensitivity and specificity in serum Tg values, serial determinations over time in the same lab assay, without interfering anti-Tg antibodies, is required.

The common follow-up paradigm for patients at low to intermediate risk of recurrence or death from thyroid cancer usually includes physical examination, TSH, Free T4, Tg, and anti-Tg antibodies every 6 months for the first 2–3 years with a thyroid ultrasound obtained 6–12 months after initial therapy, then yearly for several years [14]. This paradigm has excellent sensitivity and specificity for detection of recurrent disease in low- to intermediate-risk patients with well-differentiated thyroid cancers which make copious amounts of Tg and in whom the most likely site of recurrence is in the neck.

However, this paradigm will be less sensitive for high-risk patients with less well-differentiated tumors that may make Tg poorly and could recur outside the neck. These high-risk patients would likely benefit from additional cross-sectional imaging as part of their initial risk stratification (CT of the chest, MRI of the brain, and 18 FDG PET scanning) and occasionally as part of their follow-up disease detection management. The intensity and timing of these more aggressive follow-up studies cannot be easily proscribed in a general follow-up paradigm but requires careful individual risk assessment and follow up.

Assessing Response to Therapy

After making therapeutic interventions based on our initial risk stratification, follow-up data are obtained that should modify our initial risk assessments. In the first several years after initial therapy, serum Tg values are obtained every 6 months and neck ultrasonography is done on a yearly basis [14]. The positive and negative predictive values of these diagnostic tests can be used to either increase or decrease our initial risk estimates.

One simplistic approach to the classification of response to therapy is outlined in Table 10.4 as either excellent, acceptable, or incomplete [15, 16]. Patients with an excellent response to therapy have no detectable disease on cross-sectional imaging and undetectable serum Tg both on suppression and with stimulation. While these patients need lifelong yearly follow up, they are likely to be at very low risk of recurrence and death from thyroid cancer and can probably be followed with yearly physical examination and suppressed Tg with the occasional neck ultrasound evaluation.

Patients with an incomplete response to therapy at 6–12 months after initial therapy should be evaluated for potential additional treatment options. Most patients with incomplete response to initial therapy will benefit from additional treatments (either surgery, EBRT, or RAI). However, in some cases, patients with an incomplete response who have structural disease progression may require systemic therapy or clinical trials of novel agents.

In our experience, many patients are classified as having an acceptable, but not excellent, response to initial therapy. These patients often have low-level serum Tg on suppression (less than 1 ng/mL) or after stimulation (less than 10 ng/mL). Without identification of structural disease, it is difficult to know if this low-level Tg represents residual normal tissue or small-volume persistent thyroid cancer. In the absence of structurally identifiable disease, the natural history of many of these patients is a slow, gradual decline in serum Tg over many years without additional RAI therapy [41]. So our usual approach to these patients with acceptable response defined by low-level Tg values is cautious observation, reserving additional RAI for rising Tg values over time.

As ultrasonography becomes the cornerstone of follow up in thyroid cancer, we are identifying many patients with very small-volume disease manifest by millimeter-sized lymph nodes with abnormal ultrasonographic characteristics that probably represent residual thyroid cancer. These are often found in patients at low risk for death from thyroid cancer and either low or intermediate risk for clinically evident

Table 10.4. Response to therapy variables

	Excellent response*	Acceptable response	Incomplete response
Suppressed Tg**	Undetectable	Detectable but <1 ng/mL	>1 ng/mL
Stimulated Tg**	Undetectable	<10 ng/mL	>10 ng/mL
Trend in suppressed Tg***	Remains undetectable	Declining	Stable or rising
Anti-Tg antibodies	Absent	Absent or declining	Persistent or rising
Neck examination	Normal	Normal	Palpable disease
Neck ultrasonography	No evidence of disease	Nonspecific changes in thyroid bed Probable inflammatory lymph nodes Stable millimeter-sized cervical LN even if abnormal by US criteria	Evidence of structurally significant recurrent/persistent disease in the thyroid bed (>1 cm) Cervical lymph nodes (>1 cm), or distant metastases, particularly if structurally progressive or FDG avid
Diagnostic RAI WBS****	No evidence for RAI avid disease	No evidence for RAI avid disease Very faint uptake in thyroid bed only	Persistent/recurrent RAI avid disease present
Cross-sectional imaging (MRI, CT)****	No evidence of disease	Nonspecific changes	Structural disease present
FDG PET scanning****	No evidence of disease	Nonspecific changes consistent with normal variants or inflammatory changes	FDG avid disease present

*Patients deemed to have an excellent or acceptable response to therapy generally warrant observation without additional specific therapy, while patients with an incomplete response are likely to require additional evaluation and treatment.
**Stimulated and suppressed Tg value cutoffs optimized for patients treated with total thyroidectomy and RAI remnant ablation.
***While most sensitive and specific in patients s/p total thyroidectomy and RAI remnant ablation, a rising Tg over time should also prompt further evaluation in patients treated with less than total thyroidectomy or with total thyroidectomy without RAI remnant ablation. This highlights the crucial importance of measuring serum Tg in the same laboratory in order to ensure comparability amongst samples over time.
****While these studies are not routinely recommended for all patients without additional high-risk features or clinical suspicion of persistent/recurrent disease, results from these studies can be used as additional response to therapy measures if done.

recurrence on initial staging. While the first inclination would be toward an aggressive surgical approach to any identifiable disease, we must carefully weigh the risks associated with lymph node dissection with the potential benefit of removing very small-volume disease. Just as with low-level Tg positivity, we follow these small abnormal lymph nodes (<1 cm) with serial ultrasounds (every 6–9 months), reserving intervention for structural disease progression. Because FDG PET positivity is a predictor of more aggressive clinical outcomes, we have a lower threshold for surgical resection of PET-positive lesions than for similar-sized lesions that are not FDG avid.

Conclusion

Individualized thyroid cancer management requires a careful initial risk stratification that can accurately estimate the risk of recurrence and the risk of death from thyroid cancer. This initial risk stratification should guide our initial treatment recommendations with regard to extent of initial surgery, need for RAI ablation, degree of TSH suppression, need for external beam irradiation, and potential role of systemic therapy.

The selection of follow-up studies to detect recurrent/persistent disease should be based on

both the initial risk stratification and an understanding of the likely sites of recurrence. This risk-adapted approach will allow the clinician to tailor the aggressiveness of therapy and follow up to the risk of recurrence and death in individual patients.

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11

Medullary Thyroid Cancer

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Introduction

First described in 1959, medullary thyroid cancer (MTC) currently accounts for 5–10% of all thyroid cancers. MTC consists of a spectrum of disease that ranges from an extremely indolent tumor that can go unchanged for years to an aggressive variant that is associated with a high mortality rate. The majority of MTC are sporadic, but up to 25% of MTC are due to a germline genetic mutation. Hereditary MTC can be seen in isolation [familial MTC (FMTC)] or as part of the multiple endocrine neoplasia syndrome type 2 (2A or 2B).

MTC originates from the parafollicular C-cells of the thyroid gland. The C-cells are derivatives of the neural crest that during development incorporate into the lateral thyroid anlages. C-cells are located throughout the thyroid gland, but the majority of C-cells are located at the junction of the upper third and lower two thirds of the thyroid gland. C-cells secrete a variety of peptides and hormones; the most common of which is calcitonin. Other substances secreted by the C-cells include carcino-embryonic antigen (CEA), corticotrophin, somatostatin, vasoactive intestinal peptide, and serotonin. Calcitonin has proven to be the most useful clinical marker, because calcitonin levels correlate well with tumor burden. This makes calcitonin an ideal marker for following patients longitudinally after tumor resection. An elevated or rising calcitonin level is often the first sign of recurrent or persistent disease. CEA is also used as a marker of disease, and may be preferentially expressed in less differentiated tumors.

Pathologically, MTCs are whitish-gray in color and firm to palpation (Fig. 11.1). In sporadic cases, the tumors are usually unifocal, but in hereditary disease tumors are frequently multifocal and bilateral. Histologically, MTC forms nests of uniform cells that are characterized by the presence of stromal amyloid (Fig. 11.2). Several histologic features are associated with more aggressive disease including vascular invasion, lymphatic invasion, invasion of the thyroid capsule, and extranodal spread of the tumor.

C-cell hyperplasia is seen in many patients with hereditary disease and is felt to be a precursor to malignant transformation. C-cell hyperplasia is defined as more than six C-cells per follicle or more than 50 C-cells per low power field. Despite its clear association with malignancy in hereditary disease, the significance of C-cell hyperplasia in nonhereditary disease is uncertain.

FMTC is inherited in an autosomal dominant pattern, with variable expressivity and penetrance. The genetic mutation is found in the RET (REarranged during Transfection) protooncogene, which in 1991 was mapped to chromosome 10q11.2. The RET gene encodes a transmembrane tyrosine kinase receptor. Since RET is a protooncogene, only a single-point

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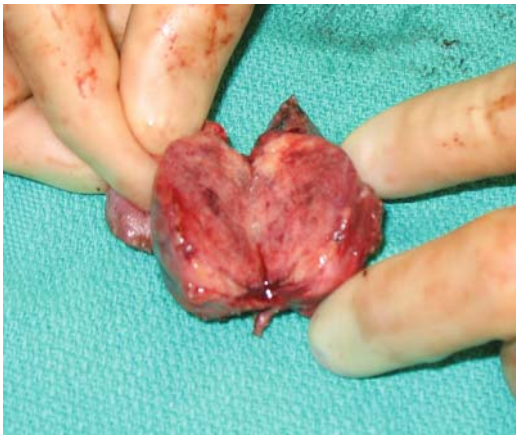

Fig. 11.1. A lymph node metastases from medullary thyroid cancer. The node is firm to palpation and the cut surface reveals the characteristic chalky-white appearance.

mutation is required for malignant transformation. In patients with hereditary disease, this point mutation is in the germline, but sporadic cases have been found to have somatic mutations of RET in 25–45% of cases. The first germline mutation of the RET gene was identified in patients in 1993, and since that time there has been a growing number of RET mutations that have been associated with hereditary MTC. The most common mutation in MEN2A is in codon 634 occurring in 80% of patients. The codon most frequently associated with MEN2B is a codon 918 mutation.

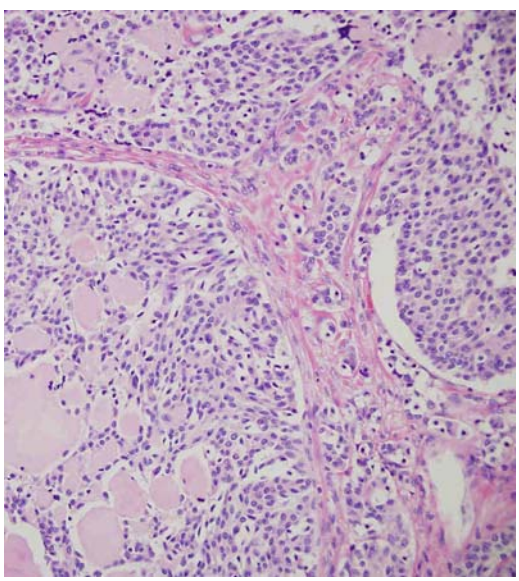

Fig. 11.2. Histologic view of medullary thyroid cancer (20× magnification), displaying the characteristic stromal amyloid deposition.

Diagnosis

Almost all patients with MTC, who are not detected through genetic screening, present with a palpable neck mass. Sporadic disease tends to present in the fifth or sixth decade of life and there is a slight female preponderance. The disease has spread to the lymph nodes in 35–50% of patients at initial diagnosis, so frequently the neck mass that is appreciated is actually a metastatic lymph node. Neck ultrasound should be performed as part of the initial evaluation to look both for additional thyroid tumors as well as the presence of suspicious neck lymphadenopathy.

Given the posterior location of many of these tumors, they can compress or invade local structures and patients can present with complaints of hoarseness, dysphagia, or respiratory difficulty. As with all patients with thyroid cancer, direct laryngoscopy should be performed to evaluate vocal cord mobility as part of the preoperative evaluation. Calcitonin levels, if markedly elevated, can cause symptoms including flushing, diarrhea, and weight loss. If patients have MEN2, they may present with symptoms of either pheochromocytoma (headaches, palpitations, or sweating) or hyperparathyroidism (fatigue, bone pain, or kidney stones).

Distant metastases are present in 10–15% of patients at the time of diagnosis [1]. The most common locations for metastatic disease include the mediastinum, liver, lungs, and bone. A contrast-enhanced CT of the chest, mediastinum, and abdomen is recommended as part of the metastatic evaluation of a patient with an initial diagnosis of MTC. Metastatic lesions may be large and calcified and readily apparent on imaging, but can also display a military pattern of small micrometastases that are unable to be seen on imaging. Bone metastases may present with pain or fractures.

Screening for known RET mutations and sequencing of DNA looking for rare RET

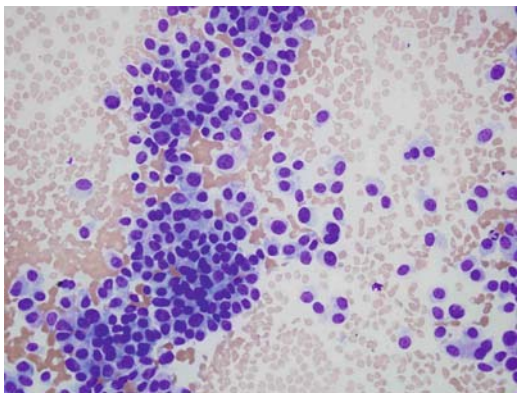

Fig. 11.3. Fine needle aspiration of medullary thyroid cancer.

mutations are now readily available. Subsequently, many patients with hereditary disease are now identified through genetic screening of at-risk individuals. Family members of patients with a germline mutation of the RET gene have a 50% chance of inheriting the mutation. If patients are identified to be genetic carriers, their lifetime risk of malignancy approaches 100%. Even patients with apparently sporadic disease have a significant chance of having a germline RET mutation and should undergo genetic testing and screening for pheochromocytoma.

The diagnosis of MTC is most frequently obtained from a fine needle aspiration (FNA) of a new thyroid nodule. On FNA, MTC is characterized by the presence of stromal amyloid and the absence of thyroid follicles (Fig. 11.3). If a FNA of the thyroid does not reveal thyroid follicles, then it should be stained for calcitonin, chromogranin A, or CEA which can confirm the diagnosis of MTC. If immunohistochemistry is not performed, it is not uncommon for an FNA of a MTC to be misinterpreted as a parathyroid tumor or a poorly differentiated thyroid carcinoma.

Serum Markers

If a patient has a clinical history or FNA that is suspicious for MTC, serum calcitonin levels can be useful to confirm the diagnosis. Calcitonin levels may be slightly elevated in a small percent of normal patients, but most patients with an elevation >100 pg/ml have a diagnosis of MTC [2]. In patients with borderline basal calcitonin levels, a stimulated calcitonin can be obtained to help clarify the diagnosis. Stimulated calcitonin levels are obtained after the administration of either calcium gluconate (2 mg/kg) or pentagastrin (0.5 μg/kg). Pentagastrin is currently only available in the USA on experimental protocols. Prior to widespread genetic testing, basal and stimulated calcitonin testing was the standard for following patients at risk for MTC. Testing was started at age 5 and performed annually until 35 years of age. The administration of pentagastrin and calcium is associated with the development of nausea, diaphoresis, agitation, and urinary urgency. Given the unpleasant side effects, many patients were noncompliant with long-term follow up, and this technique has largely been abandoned.

The degree of calcitonin elevation correlates well with tumor burden. Nodal metastasis starts emerging at basal calcitonin levels of 10–40 pg/ml (normal range <10 pg/ml). Distant metastases are typically associated with calcitonin levels of greater than 150 pg/ml and frequently >1000 pg/ml [3]. Patients with calcitonin levels >3000 pg/ml are likely to have extensive metastatic disease and are unlikely to be cured of their disease [4]. If patients have a preoperative calcitonin level less than 50 pg/ml, they have a 98% chance of achieving an undetectable calcitonin level with surgery alone [5].

Some groups have advocated routine serum calcitonin testing in all patients with a new thyroid nodule. Unfortunately, falsely elevated calcitonin levels can be seen in both autoimmune thyroiditis and multinodular goiter, causing up to 4% of patients to have elevated basal calcitonin levels. Further evaluation of patients with elevated basal calcitonin levels reveals that only 5% actually have MTC (95% false positive)[2]. Since most of the MTC that is detected by serum calcitonin measurements is also picked up by FNA, the diagnostic yield of routine calcitonin measurement appears to be very low, identifying only one new diagnosis out of 1383 patients [2]. Although early diagnosis affords these patients earlier intervention and perhaps improved outcomes, the cost effectiveness of routine calcitonin screening must be carefully examined.

CEA has also proven to be a useful tumor marker in patients with MTC. CEA levels are elevated in >50% of patients with MTC.

Preoperative CEA levels can be useful for risk stratification of patients. A preoperative serum CEA level >30 ng/ml is highly predictive of inability to cure a patient with operative intervention [6]. CEA levels >100 are highly associated with extensive lymph node involvement and distant metastasis. An increasing CEA level in the presence of a stable calcitonin can be a sign of dedifferentiation of the tumor and is associated with a worse prognosis.

Other tumor markers, such as plasma catecholamines, serotonin, and chromogranin A, may be elevated in patients with MTC; however, their clinical utility is limited [7]. Plasma calcitonin and CEA are the most useful markers for following patients with MTC and should be obtained in all patients.

Associated Conditions

While the majority of MTC is sporadic, approximately 20% of cases are due to a hereditary form of the disease. The hereditary forms of MTC are MEN2A, MEN2B, and FMTC. All of these disorders are inherited in an autosomal dominant pattern and have variable penetrance. MEN2A is the most common disorder and accounts for 75% of hereditary MTC.

MEN2A is associated with MTC in >95% of cases. The MTC in MEN2A is typically multifocal and bilateral. The age of onset varies with the specific genetic mutation, but it typically presents in early adulthood. Pheochromocytomas can be seen in up to 50% of cases and they are frequently multifocal and associated with adrenal medullary hyperplasia. Pheochromocytomas can be screened for using either plasma metanephrines or 24-h urine collections for catecholamines and metanephrines. If identified, pheochromocytomas should be treated and resected prior to proceeding with a neck operation. Preoperative alpha blockade should be initiated and blood pressure normalized prior to proceeding with a laparoscopic adrenalectomy. Hyperparathyroidism occurs in 20–35% of patients with MEN2A and is most common in patients with codon 634 mutations. Screening for hyperparathyroidism can be performed with annual calcium and parathyroid hormone (PTH levels). While historically felt to be due to hyperplasia, the disease is frequently very asymmetric and may be due to a single enlarged gland. Patients should be treated as other patients with primary hyperparathyroidism with removal of only the grossly abnormal parathyroid glands. Some variants of MEN2A are also associated with either cutaneous lichen amyloidosis or Hirschsprung's disease. Most of the mortality associated with MEN2A is from the MTC, therefore early recognition and treatment is essential.

In MEN2B, nearly 100% of patients develop MTC. MTC develops at a very young age (infancy) and has a very aggressive course. Because of the early age of onset and the frequent delay in diagnosis, patients with MEN2B are rarely cured of their disease. Pheochromocytomas are seen in 50% of patients, but no patients develop hyperparathyroidism. A distinguishing feature of MEN2B is the development of diffuse ganglioneuromas of the lips, tongues, eyelids, and gastrointestinal tract. These patients have a characteristic appearance including a marfanoid habitus, everted eyelids, and thick lips. These patients also have problems with megacolon, skeletal abnormalities, and markedly enlarged peripheral nerves. Due to the aggressive nature of the MTC in these patients, many die at a young age and never reproduce. Therefore, most of the MEN2B diagnoses seen today are de novo germline mutations.

Familial MTC occurs when families develop only MTC. Since there is significant overlap in the genetic mutations that lead to either FMTC or MEN2A, the definition of FMTC is strict. In order to consider a family to have FMTC and not MEN2A, there must be no evidence of either pheochromocytoma or hyperparathyroidism in more than 10 carriers and multiple members need to be affected after the age of 50. Since MTC is often the first manifestation of MEN2A, with pheochromocytomas lagging significantly behind, distinguishing between MEN2A and FMTC can be difficult. Especially in smaller kindred it is safer to label a family as MEN2A than FMTC, which ensures that patients are screened and monitored for the development of pheochromocytomas.

Since the results of genetic testing may not be available prior to operative intervention, every patient must be evaluated for a potential pheochromocytoma. Pheochromocytoma can be tested for with either plasma metanephrines or a 24-h urine collection for catecholamines, metanephrines, and vanillyl mandelic acid.

It is essential to rule this out prior to proceeding with general anesthesia, as an undiagnosed pheochromocytoma can provoke a life-threatening hypertensive crisis. Since hyperparathyroidism is present in 20–35% of patients with MEN2A, all patients should also have a serum calcium and PTH checked prior to operative intervention.

Genetic Testing

Germline genetic mutations in the RET gene will be found in 6–10% of patients with apparently "sporadic" MTC. Therefore, routine genetic screening should be performed in all patients with a diagnosis of MTC. Genetic testing of the RET gene is performed by PCR amplification of the patient's germline DNA usually obtained from white blood cells. Mutations are screened for in exons 10, 11, 13, 14, 15, and 16. If no mutations are found, the remaining 15 exons of the RET gene should be sequenced. Currently known mutations encode over 95% of cases of hereditary MTC. Commercial testing for the most common mutations is widely available, but more thorough analyses are required to identify the less common mutations. The predicted risk of hereditary MTC in a patient with a negative screen is estimated to be only 0.18%.[8] If patients are not found to have a RET mutation, but remain concerned about the risk of an unidentified mutation, they can be screened with periodic basal/stimulated calcitonin levels.

The significance of a genetic mutation for a patient and their family cannot be underestimated. It is important that prior to screening for genetic mutations that patients receive appropriate genetic counseling. The risks and benefits of genetic testing should be carefully discussed with the patient and their family. Patients need to understand the significance of a genetic mutation, the limitations of the testing, and the potential adverse affects (including genetic discrimination and effects on family relations). Once a patient is found to be positive for a RET mutation, they must be carefully counseled regarding the risks to additional family members. At-risk family members need to be identified and should undergo genetic testing as soon as possible. Patients that are identified as RET mutation carriers should undergo prophylactic thyroidectomy. The timing of genetic testing and prophylactic surgery should be determined after a careful assessment of the risks of malignancy and the aggressiveness of the disease associated with the genetic mutation as well as its expression within the family.

Among RET mutations, there is significant variation in the aggressiveness of the MTC that develops. As we gain a better understanding of the genotype–phenotype relationships among RET mutations, we are better able to tailor the treatment of our patients. Currently, RET mutations are classified into three groups based on level of risk (or aggressiveness) of MTC (Table 11.1).

Table 11.1. RET mutations

Risk level for MTC	Codon mutation	Youngest age of MTC	Youngest age of nodal disease	Age of prophylactic surgery
Level 3 (highest)	883	9 mo	1	Within first 6 months of life (preferably in the first month)
	918			
	922			
Level 2 (higher)	611	7		By age 5
	618	7	11	
	620	5	10	
	634	15 mo	5	
Level 1 (high)	609	5		By age 5–10
	630	1		
	768	22		
	790	10		
	791	21		
	804	6		
	891	13		

Source: Data compiled from [8, 15, 46, 47]

Patients with level 3 mutations have the most aggressive disease. Level 2 mutations are associated with a slightly later onset and a less aggressive course, while level 1 mutations are associated with the most indolent course.

Patients with mutations in codon 883, 918, and 922 are classified as level 3 mutations and have the most aggressive course, with metastatic disease presenting in the first years of life. Because of the high risk of malignancy at an early age, thyroidectomy is recommended within the first 6 months and preferably within the first month of life. Microscopic MTC is frequently seen by age 1 and metastatic disease has been reported prior to age 1. Because of the early risk of nodal involvement, patients with MEN2B should also undergo a central neck dissection [8].

Level 2 RET mutations, including codon 611, 618, 620, and 634 mutations, are considered high risk for MTC and the current recommendation is that these patients undergo thyroidectomy before age 5 [8]. Whether or not patients with MEN2A should undergo a prophylactic central neck dissection is not clear and currently there is no consensus on this issue. It is important to consider the specific mutation that the patient has as well as the course of disease within the family to estimate the risk of malignancy and nodal disease and then balance the risks and benefits of adding a nodal dissection. Codon 634 mutations are the most common cause of MEN2A and have a strong association with both pheochromocytoma and hyperparathyroidism.

Level 1 RET mutations, including codon 609, 768, 790, 791, 804, and 891, are still considered high risk for MTC, but are the lowest risk of the RET mutations. MTC in these patients tends to develop later in life and takes on a more indolent course. These patients are still best treated with a prophylactic thyroidectomy, but the optimal timing of surgery is not clear. Since clinically apparent disease is rarely reported prior to 10 years of age, many recommend waiting until then to perform the thyroidectomy. However, there remains variability and unpredictability in some families, hence many surgeons recommend treating all patients with MEN2A the same and perform their prophylactic operation by age 5 whenever possible. An alternative to using a strict age cutoff is to perform periodic stimulated calcitonin testing and to proceed to thyroidectomy when the calcitonin becomes elevated.

While the genetic mutations associated with MEN2B are distinct, there is significant overlap in the mutations that are associated with MEN2A and FMTC. MEN2A has been associated with mutations in both level 1 (790, 791) and level 2 (609, 611, 618, 620, 634) categories. FMTC has been described in all of the mutations associated with MEN2A and additionally in families with codon 532, 533,768, 804, 844, 891, and 912 mutations [9, 10].

Somatic mutations of RET have also been found in up to 25% of sporadic MTC tumors. The most common mutation is in codon 918 which is associated with a poorer patient prognosis.

Prognosis

Unlike papillary thyroid cancer, which has been increasing in incidence, the incidence and mortality from MTC has remained very stable over the last few decades [11]. Overall, the prognosis of patients with MTC is good. The 10-year survival of patients with MTC is 75–85% [12, 1, 10]. Approximately half of patients with MTC present with disease localized to the thyroid gland, and these patients have a 10-year survival of 95.6% [1]. A third of patients will present with locally invasive tumors or clinically apparent spread to the regional lymph nodes. Patients with regional disease have a 5-year overall survival rate of 75.5%. Distant metastases are present in 13% of patients at initial diagnosis and portend a poor prognosis with a 10-year survival of only 40%.

Independent prognostic factors include advanced patient age, extraglandular invasion, gross residual disease, and advanced disease stage [1, 13]. The most commonly used staging system for MTC is the TNM system, which is outlined in Table 11.2. When matched for age and stage, hereditary and sporadic patients have similar life expectancies. Calcitonin doubling time has also been proposed as a significant negative prognostic factor. Patients with calcitonin doubling times of less than 6 months have a 5-year survival of 25% in comparison to patients with a doubling time greater than 2 years who have a 100% 5-year survival [14].

Table 11.2. TNM staging of medullary thyroid cancer

Stage	Tumor size	Node status	Metastasis
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
IVB	T4b	Any N	M0
IVC	Any T	Any N	M1

Source: Reprinted from AJCC Cancer Staging Atlas, 2006, p. 73.

Tumors with minimal calcitonin staining or tumors that present with rapidly increasing CEA levels (with stable calcitonin levels) have also been shown to have a worse prognosis.

Prophylactic Surgery

Prophylactic surgery removes the at-risk organ prior to it developing clinically significant disease. When determining the timing of prophylactic surgery, it is important to balance the risk of clinically significant disease with the risks of operative intervention. In hereditary MTC, there is a clear age-related progression from C-cell hyperplasia to MTC and ultimately to nodal spread. However, the optimal timing of prophylactic thyroidectomy is not clear. Hopefully as we gain a better understanding of the phenotype–genotype relationships amongst the RET mutations, we will be better able to predict when disease is likely to develop and therefore plan operative intervention prior to that time.

The RET mutations associated with hereditary MTC are listed in Table 11.1 with guidelines as to when to perform a prophylactic thyroidectomy for each mutation. In general, it is reasonable to intervene in children with MEN2A and FMTC by age 5, while patients with MEN2B should be operated on during infancy whenever feasible. In a recent study looking at long-term follow up of patients who have undergone prophylactic thyroidectomy, no patient with MEN2A who was operated on under the age of 7 has had evidence of recurrent disease, with over 5 years of follow up [15]. If a family does not want to proceed with prophylactic surgery in a young child, then it is reasonable to follow the patient closely with stimulated plasma calcitonin levels, and then proceed with operation when there is a rise in the stimulated calcitonin levels.

The extent of surgery that is necessary in the prophylactic setting has been debated. Everyone agrees that at a minimum all patients should undergo a total thyroidectomy. The debate involves whether or not a central neck lymphadenectomy should be performed. Advocates of routine central neck dissection argue that even in screened patients, clinically occult disease with nodal metastasis can be present in 6% of patients [15]. They argue that the best opportunity to cure a patient is at their initial operation. With the use of routine autotransplantation of the parathyroid glands, the long-term complications of a central neck dissection can be minimized. Opponents of routine central neck dissection argue that while nodal disease has been seen in the occult setting, it is very rare in children under 10 [15]. They suggest that a more selective approach can be performed utilizing preoperative ultrasound and tumor markers to further risk stratify patients. With a normal preoperative ultrasound and serum calcitonin (basal and/or stimulated) and CEA level, the risk of occult nodal disease is very low and the potential benefits of a prophylactic neck dissection are outweighed by the risks of permanent hypoparathyroidism. In a recent series from Washington University where they have performed 85 prophylactic total thyroidectomies with bilateral central neck dissections (with routine parathyroidectomy with autotransplantation), they found two (2.4%) patients with nodal disease and three patients with permanent hypoparathyroidism (3.5%) [16]. While the incidence of nodal disease is low, those patients who have nodal disease at the time of their prophylactic dissection often end up having persistently elevated calcitonin levels and are not cured of their disease [15]. In order to minimize the risks of this prophylactic operation, it is essential that these procedures be performed only by experienced surgeons.

Since the first prophylactic thyroidectomies were performed in the early 1990s, the risk of recurrence after a prophylactic thyroidectomy

is still unknown. Preliminary results suggest that the risk of recurrence is very low, especially when surgery is performed prior to age 10 [15]. However, since the long-term outcomes are not known, it is recommended that after a prophylactic thyroidectomy, patients be followed every 1–2 years with plasma calcitonin and CEA levels. In addition, patients at risk for MEN2 need to be screened for the development of both pheochromocytoma (MEN2A and 2B) and hyperparathyroidism (MEN2A only), which can occur decades later.

Clinically Evident Disease

Patients who have clinically evident disease are best treated with a minimum of a total thyroidectomy and bilateral central neck dissection. Ipsilateral lateral neck dissection should be added if the primary tumor is greater than 1 cm in size or there is evidence of positive nodes in the central neck. A contralateral lateral neck dissection should be considered in patients with bilateral tumors or extensive lateral adenopathy on the side of the tumor (Fig. 11.4).

Central neck nodal disease is present in up to 81% of patients with palpable tumors [17]. Addition of a central neck dissection improves cure rates over a thyroidectomy alone in patients with clinically evident MTC [18]. A central neck dissection consists of a complete clearing of all lymph nodes and fibrofatty tissue from the level VI compartment. Level VI extends from the hyoid bone superiorly to the innominate vessels inferiorly; laterally it is bound by the carotids. A level VI lymphadenectomy requires careful

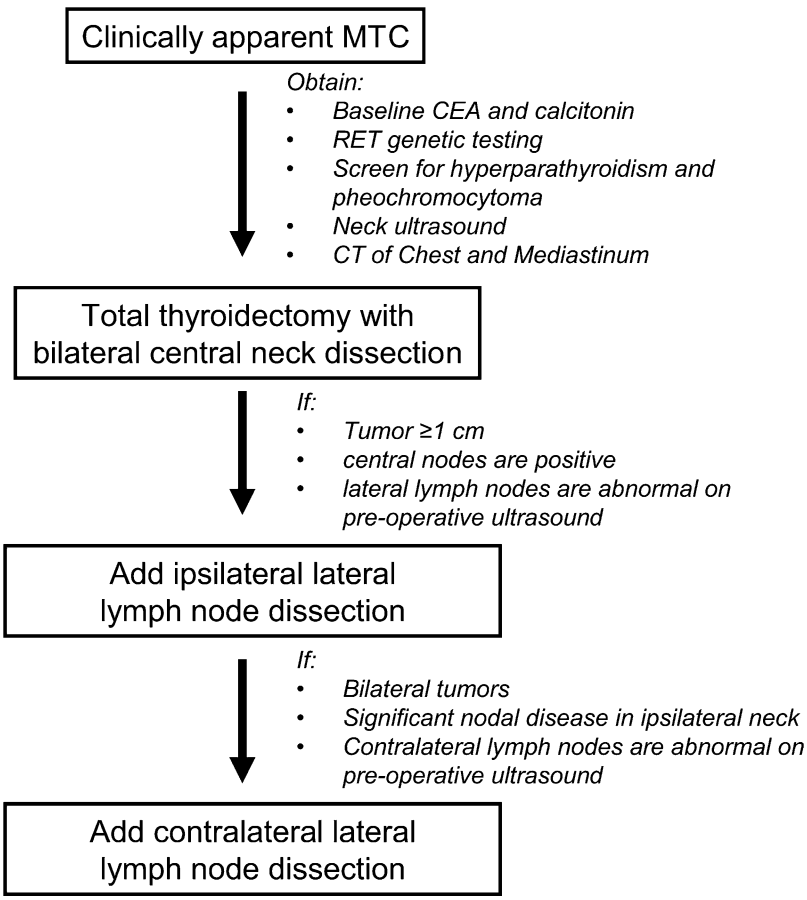

Fig. 11.4. An algorithm for the treatment of clinically apparent MTC.

dissection of the recurrent laryngeal nerve along its entire length; it also requires meticulous dissection of the parathyroid glands. Many surgeons argue that it is impossible to do a complete central neck dissection without removing the parathyroids and/or their blood supply. Some surgeons routinely remove the parathyroid glands with the specimen and then carefully dissect them free from the nodal tissue and autotransplant them. If patients have sporadic MTC, FMTC, or MEN2B, then the autotransplant can be performed in the sternocleidomastoid. In patients with MEN2A, due to the risk of hyperparathyroidism in the remnant, the parathyroid tissue should be autotransplanted to the nondominant forearm. Placement of the autograft in the forearm facilitates the work-up and management of any hyperparathyroidism that may develop. Autotransplanted parathyroid glands usually do not function for 4–8 weeks, so calcium and vitamin D replacement is required during this period of recovery.

The role of a lateral dissection in MTC is less clear. Ipsilateral nodal metastasis are present in 14–80% of patients, [17, 19] and contralateral lateral nodal metastasis have been reported in 19–49% of patients [17, 20]. Since there is a high incidence of lymph node disease, even in tumors <1 cm, some surgeons advocate a bilateral lateral neck dissection for all patients with MTC [20, 17]. Unlike papillary thyroid cancer, where microscopic nodal disease may be effectively treated with radioactive iodine, the only effective treatment for MTC is surgical resection. While many patients with MTC have an indolent course, some patients suffer from a much more aggressive variant of disease, and early surgical intervention gives them the best chance for a long-term cure. The significance of microscopic disease in the lymph nodes is not fully known, but a significant number of patients will have recurrent or persistent disease based on the presence of an elevated calcitonin after primary operation. Despite an aggressive surgical resection of all neck lymph nodes, only 32% of patients with nodal disease at the time of their operation have undetectable calcitonin levels postoperatively [20].

The morbidity of a bilateral neck dissection can be significant, and because of this, many surgeons advocate a more selective approach to the lateral neck. Preoperative neck ultrasound is highly sensitive for detecting lateral lymphadenopathy. An ipsilateral lateral lymphadenectomy is advocated when ultrasound or physical exam suggests the presence of lateral lymphadenopathy, when central compartment lymph nodes are involved, or when the primary tumor is ≥ 1 cm. Contralateral lateral neck dissections are then added when patients have bilateral tumors or there is extensive lymphadenopathy on the primary tumor side. Contralateral lymph node involvement is almost never seen in the absence of ipsilateral lymph node disease; therefore in patients with a unifocal tumor and no ipsilateral lymph node disease, there is likely no benefit to a contralateral neck dissection [20]. Lateral neck dissections can be performed at the time of the initial total thyroidectomy and central neck dissection or can be done in a staged procedure after the initial operation.

Recent NCCN guidelines [21] recommend that patients who have demonstrable MTC or MEN2B should be treated with a total thyroidectomy with bilateral central neck dissection. Ipsilateral lateral neck dissections should be added in patients with primary tumors ≥ 1 cm or if the central nodes are involved. Interestingly, according to the SEER database, over half of patients treated for MTC over the last several decades had less than the recommendation operation, suggesting that many patients with persistent calcitonin elevations may have had an inadequate initial operation [1, 22].

Postop Surveillance

Patients with disease confined to the thyroid gland without nodal disease have a very low risk of recurrence and rarely die of their disease [23]. However, many patients with MTC have nodal disease at presentation, and these patients have a very high risk of developing recurrent or persistent disease. Therefore, they must be followed closely postoperatively.

Follow up should start 2–3 months postoperatively by obtaining a new baseline calcitonin and CEA. However, if values are markedly elevated preoperatively, it may take up to 4 months to clear, so if the levels are still elevated at 2–3 months, they should be repeated prior to pursuing further work-up. Patients who have undetectable calcitonin levels postoperatively can be followed with annual measurements of serum calcitonin and CEA. Routine cervical

ultrasound can be added, but is of no proven benefit. If there is a rise in serum markers, then additional imaging can be pursued as indicated. There is no one combination of tests that best serves all patients. A reasonable algorithm can be determined after considering the individual patient as well as the quality of studies available at your institution. Thyroid hormone replacement is required after a total thyroidectomy; however, TSH suppression is not indicated in patients with MTC.

Persistent/Recurrent Disease

The natural history of MTC varies greatly. Some patients have a very indolent disease course and may live years with a mildly elevated calcitonin level with no imageable disease. Then there are others who present with a very aggressive variant, that is widely metastatic and/or locally invasive and these patients warrant a more aggressive surgical approach to minimize their risk of dying of their disease.

Patients with MTC must be followed closely as approximately 50% of patients will develop recurrent disease. Calcitonin and stimulated calcitonin levels are very sensitive ways for detecting either residual or recurrent disease. When the postoperative calcitonin level is elevated, a careful examination must be performed prior to proceeding with operative exploration. Patients with isolated cervical disease may be operated on for a curative intent, but patients with metastatic disease should only undergo operative intervention for palliative reasons. Therefore, it is essential to perform a thorough search for metastatic disease prior to embarking on a neck reexploration.

Since surgery is the mainstay of therapy for MTC, an adequate initial operation is essential in order to optimize patient outcomes. However, approximately 50% of patients treated in the USA each year undergo an inadequate initial operation and many of these patients are found to have persistently elevated calcitonin levels postoperatively. Patients with an inadequate initial operation may be best served with a repeat neck operation.

In order to optimize outcomes and potentially cure patients of their disease, some surgeons advocate a very aggressive approach for the treatment of persistent disease after an inadequate initial surgery. Using a technique of "microdissection" of all compartments of the neck, Tisell and colleagues [24] were able to normalize calcitonin levels in one third of patients and substantially reduce them in an additional third. Other more recent studies have confirmed that with good patient selection, neck reoperation can normalize calcitonin levels in about a third of patients and significantly reduce levels in 40% of cases [25]. The key to successful neck reoperation is careful patient selection and recognition of metastatic disease. Evaluation of metastatic disease can include anatomic imaging with neck US, CT scan of the chest and abdomen, and MRI of the neck and mediastinum. Functional imaging can also help to identify distant sources of disease. Both PET and MIBG scans have been used to localize metastatic disease in patients with MTC. Since these tumors produce CEA, an anti-CEA-labeled antibody scan has also been utilized.

Often metastatic disease to the liver takes on a miliary pattern and is not detectable by conventional imaging. Therefore, some have advocated the use of more invasive studies as part of the metastatic work-up. Selective venous catheterization can be performed to obtain basal and/or stimulated calcitonin levels from various sites in the neck, chest, and abdomen. If disease localizes to the neck, then patients can be successfully treated with surgical resection of the appropriate neck region. While small reports have found this technique to be beneficial, others have found that hepatic measurements can be spuriously elevated and misleading, bringing to question the utility of this method of evaluation [16]. Since most patients with persistently elevated calcitonin levels either have neck disease or metastatic disease to the liver, some advocate doing a diagnostic laparoscopy to examine the liver surface prior to cervical reoperation. Using routine laparoscopy to evaluate the liver, one group found that 21.3% of patients had occult liver disease that altered the approach to the patient's cervical disease [26].

Neck reoperations are associated with significant risks. Therefore, reoperation should only be pursued if there is significant likelihood of benefiting the patients. If patients had an inadequate initial operation or are found to have only locoregional disease, then surgical resection should be pursued. Patients with tracheal or mediastinal

invasion can die of local compression/invasion if the disease is not resected. Therefore, if patients develop symptomatic locoregional recurrence, even in the setting of metastatic disease, then they should be offered surgical resection when feasible and external beam radiation when surgery is not possible [27].

If a patient had an adequate first operation and postoperatively they have persistently elevated calcitonin, but all imaging is negative, it is appropriate to follow them clinically without further intervention. These patients should be followed annually and reimaged if there is a progressive increase in the serum markers.

Radiation Therapy

External beam radiation does not currently play a significant role in the treatment of patients with MTC. The primary treatment modality for all patients who are candidates is surgical resection. However, radiation therapy has been applied to help palliate local disease when surgery is not a feasible option. Radiation therapy has also been used to palliate bony metastases. Given the high risk of cervical recurrence in these patients, especially those with microscopic residual disease, nodal involvement, or extraglandular spread, some have advocated for postoperative treatment with external beam radiation. There have been several studies examining the role of adjuvant external beam radiation in MTC. One study found that in high-risk patients, surgery plus external beam radiation had a recurrence rate of 14% compared to 48% in the surgery alone group [13]. While this study suggests that a subset of patients may benefit from adjuvant external beam radiation, this needs to be further evaluated.

Despite the paucity of evidence regarding the utility of postoperative radiation therapy, a significant number of patients are treated with it. Interestingly in a recent review of the SEER database, 18% of patients were treated with adjuvant radiation. Radiation therapy not only didn't improve survival, but it was associated with decreased survival [1]. External beam radiation causes extensive scarring and fibrosis within the neck making future surgical interventions both difficult and potentially dangerous. Since the benefits of radiation therapy are not clear and its use limits future surgical intervention, its use should be reserved for cases of known residual disease in which complete surgical resection is not possible.

Radioactive iodine is part of the standard treatment for papillary thyroid cancer, but since C-cells are not of thyroid follicular origin, radioactive iodine is not taken up in the C-cells and radioactive iodine treatment plays no role in the management of MTC. Interestingly, there has been some interest in using radioactive iodine, not to treat significant disease, but to ensure that all C-cell containing thyroid tissue was removed during the initial operation [28]. After a total thyroidectomy, even in the most experienced hands, there is a small amount of residual thyroid tissue, which may contain C-cells, which theoretically could form a new focus of MTC in a patient with a germline predisposition. Radioactive iodine is only taken up by thyroid follicle cells but affects tissue in the surrounding 2 mm of tissue via ß-ray emission. One small study has suggested that in patients with disease confined to the thyroid, who have an elevated calcitonin level postoperatively, radioactive iodine may decrease calcitonin levels [28]. While interesting, further studies need to be performed to clarify the possible role of radioactive iodine in the treatment of MTC in this subset of patients.

Radioimmunotherapy has been proven efficacy in other neuroendocrine tumors and several targets have been investigated in MTC. CEA and Somatostatin receptors are both present on MTC cells. A preliminary study using anti-CEA-targeted radioimmunotherapy has shown some efficacy in high-risk patients (calcitonin doubling times <2 years) in comparison to historical controls. Unfortunately this therapy is associated with significant toxicity including grade four neutropenia and thrombocytopenia in $>20\%$ of patients[14, 29].

Systemic Therapy

Surgery has been the mainstay of therapy for patients with MTC. An aggressive surgical approach has been advocated because once patients develop systemic disease, treatment options are very limited.

Conventional chemotherapy has shown limited efficacy in patients with MTC. Complete responses are very rare and partial responses have been seen in less than a third of patients. The side effect profile of chemotherapy is often

substantial, making this an unappealing option for many patients. Single-agent regimens using doxorubicin, dacarbazine, capecitabine, and 5-fluorouracil have been reported with partial response rates up to 24–29% [30]. Newer chemotherapeutic agents, such as Irinotecan (a topoisomerase I inhibitor) and 17-AAG (heat shock protein 90 inhibitor), are currently being evaluated in phase II clinical trials.

Patients with metastatic disease can have significant symptoms from calcitonin excess including severe flushing, diarrhea, and weight loss. Patients with hormonal symptoms may benefit from medical treatment with somatostatin analogs. These patients may also benefit from cytoreductive surgery of unresectable disease. Procedures to decrease the tumor burden, including resection and ablation, may provide patients with significant symptomatic relief [27].

With the discovery of the RET protooncogene and its integral role in the pathogenesis of MTC, a new class of therapies have developed aimed at the molecular pathways central to the development and progression of MTC. RET is part of the receptor tyrosine kinase family. RET has been shown to signal through multiple downstream pathways including ERK, PI3K/AKT, p38 MAPK, and JNK [4]. While present investigations and therapies aim to block the tyrosine kinase at the receptor level, there is significant potential for developing more focused therapies as we gain a better understanding of the critical downstream targets of these receptors.

Recently, a new class of drugs has been discovered that act as tyrosine kinase inhibitors. The first commercially available receptor tyrosine kinase inhibitor was imatinib mesylate (Gleevec), which has been used successfully in the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors. An initial phase II study with Gleevac in MTC has shown limited efficacy with no responses in 15 patients and significant toxicity [31].

Many of the tyrosine kinase inhibitors that are now being investigated inhibit multiple receptors, including RET, EGFR, and VEGF. A tyrosine kinase inhibitor that show significant inhibition of the RET receptor tyrosine kinase has been identified and is currently in phase II clinical trials. This drug, initially labeled ZD6474 and now referred to as Vandetanib (Zactima), is available in an oral form and has been shown to have efficacy in inhibiting the RET receptor. Vandetanib is currently being evaluated in a multicenter phase II clinical trial for patients with hereditary MTC. Preliminary results have been presented in abstract form and reveal a 20% partial response and a 30% stable response by CT imaging [32]. However, there was a much more dramatic decrease in tumor markers. Plans are underway to expand this trial to sporadic MTC as well.

Several other receptor kinase inhibitors are also undergoing evaluations in clinical trials, many of these trials have not been published but preliminary results have been presented and there appears to be some efficacy in patients with metastatic MTC. Motesanib diphosphate (AMG 706) is a multikinase inhibitor that is currently in phase II clinical trials. AMG 706 targets VEGF, PDGF, RET, and Kit receptors. It is currently being evaluated in both advanced differentiated thyroid cancer and advanced MTC. Results from the MTC portion of the trial are not available yet, but some antitumor activity was seen in patients with differentiated cancer [33]. Sorafenib (BAY 43-9006), another RET kinase inhibitor currently in phase II trials, has been shown to cause a dramatic reduction in calcitonin levels and leads to marked symptomatic improvement in patients with metastatic disease. In addition, no patient on Sorafenib had progression of disease [34]. Interestingly, many of these new therapies lead to dramatic reductions in calcitonin levels almost immediately, suggesting that tumor markers may not be a reliable way to monitor tumor response to therapy.

Future Therapies

Many of these tyrosine kinase inhibitors lack receptor specificity, therefore their true mechanism of action is not clearly known. Several signaling pathways, such as the phosphatidyl-inositol 3-kinase (PI3K)/Akt, mitogen-activated protein kinases (MAPKs), and Notch1/Hairy Enhancer of Split-1 (HES-1)/achaete-scute complex like-1 (ASCL1) signaling pathway, have also been shown to play important roles in regulating the growth of neuroendocrine tumors (NETs)[35–39] Thus, another potential therapeutic target could be manipulation of these various cellular signaling pathways.

Notch1 signaling is very minimal or absent in prostate cancer, and NETs such as small cell lung

cancer (SCLC), carcinoid, and MTC [35, 36, 40, 41]. Activation of Notch1 significantly reduced the growth of MTC (TT) cells and regulates calcitonin levels in a dose-dependent manner. These observations support the hypothesis that Notch1 functions as a tumor suppressor in MTC tumors and cell lines. Recently, we and others have reported that Raf-1 activation in a MTC(TT) cell line results in growth suppression as well as reduction in NE hormones (such as calcitonin and serotonin) and levels of the RET protooncogene [42, 43, 39]. We have explored the possibility of pharmacologically activating raf-1 in MTC cells. Though the compound ZM336372 was originally identified as a small molecule inhibitor of Raf-1 [44], recently we have shown that it activates raf-1 pathway in NET [37, 45]. Recently we have observed that treatment of MTC cells with ZM336372 resulted in growth inhibition suggesting that activation of raf-1 pathway is required for the antitumor proliferation effect (Kunnimalaiyaan et al., manuscript in submission). Given the important role of Notch1 and raf-1 in the regulation of growth of MTC, we hope that activating compounds for these signaling pathways will have novel and potent therapeutic value for the treatment of patients with MTC.

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12

Technique of Thyroidectomy

Hélène Gibelin, Thibault Desurmont, and Jean-Louis Kraimps

Introduction

Thyroid surgery is the most common operation in endocrine surgery. Total extracapsular lobectomy with isthmusectomy (isthmolobectomy) is the procedure of choice. The entire lobe and the isthmus, including the pyramidal lobe, must be removed.

Subtotal lobectomy should be avoided since reoperation to complete a lobectomy is associated with a greater risk of injury to the recurrent laryngeal nerve (RLN) and parathyroid glands. Consequently, subtotal lobectomy is considered an inadequate operation. Thyroid surgery can and should be a safe procedure with minimal morbidity and negligible mortality. An accurately performed operation on thyroid gland requires both experience and technical ability [1, 2]. This emphasizes the importance of skilled Departments in Endocrine Surgery, performing a great number of procedures and teaching the youngest surgeons and residents [3]. It is the best way to minimize incidence of complications.

The general rules of thyroid operation are as follows:

- Good exposure (by conventional approach or with the endoscope in mini-invasive approaches). Excellent visualization is the main way to avoid RLN or parathyroid injury.
- Systematic identification of anatomic structures and meticulous dissection [4]. Thyroid operation without identification RLN or parathyroid glands does not make sense. Consequently, bleeding should be avoided; if the latter occurs, identification of these anatomic structures is absolutely required before hemostasis avoiding diathermy, even bipolar.
- Before surgery, the patient should be informed about the reasons why an operation is needed, the alternative methods of treatment that might be used, and the potential risks and benefits of the procedure. Information about possible complications must be given to the patient and clearly explained before surgery.
- The patient should undergo a thorough medical evaluation to be sure that he or she is euthyroid.

Isthmolobectomy

The patient is carefully positioned on the operating table with the neck hyperextended. A rolled towel is placed under the shoulders which allows sufficient neck extension. A sponge ring is placed under the occiput for adequate head support and to keep it from moving. The eyes should be carefully taped shut to avoid corneal abrasions.

Disinfection is performed with an alcoholic agent without iodine, which might interfere with postoperative radionuclear scanning and ablative therapy.

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Slight elevation of the head of the operating table is helpful in decreasing venous congestion.

The surgical field is draped from below the sternal notch to the chin and laterally on posterior part of the sternocleidomastoid muscles.

Skin Incision

The standard Kocher's incision must be used. It is a collar-type incision placed transversally along the Langer's line of the skin. This yields an excellent cosmetic result. The length of the incision must be adapted to the thyroid size. Most often a 4- to 5-cm incision allows safe thyroidectomy, but a larger incision can be necessary in case of large goiters or short neck. The surgical incision should therefore be made about 1 cm caudal to the cricothyroid cartilage since it then will be centered directly over the thyroid gland.

The skin incision should be made perpendicular to the patient and carried down through the subcutaneous tissue and platysma muscle with preservation of the anterior jugular veins.

The skin, subcutaneous fat, and platysma muscle should be mobilized as two flaps upward to the thyroid cartilage and downward to the sternal border (see Fig. 12.1). Once these flaps have been mobilized, skin towels are applied, as well as a self-retaining retractor.

Strap Muscles

The next step is the dissection in the midline of the neck between the strap muscles from the thyroid cartilage to the suprasternal notch. Sternohyoid and sternothyroid muscles are dissected and retracted using right-angle retractors. The middle thyroid vein is identified, ligatured,

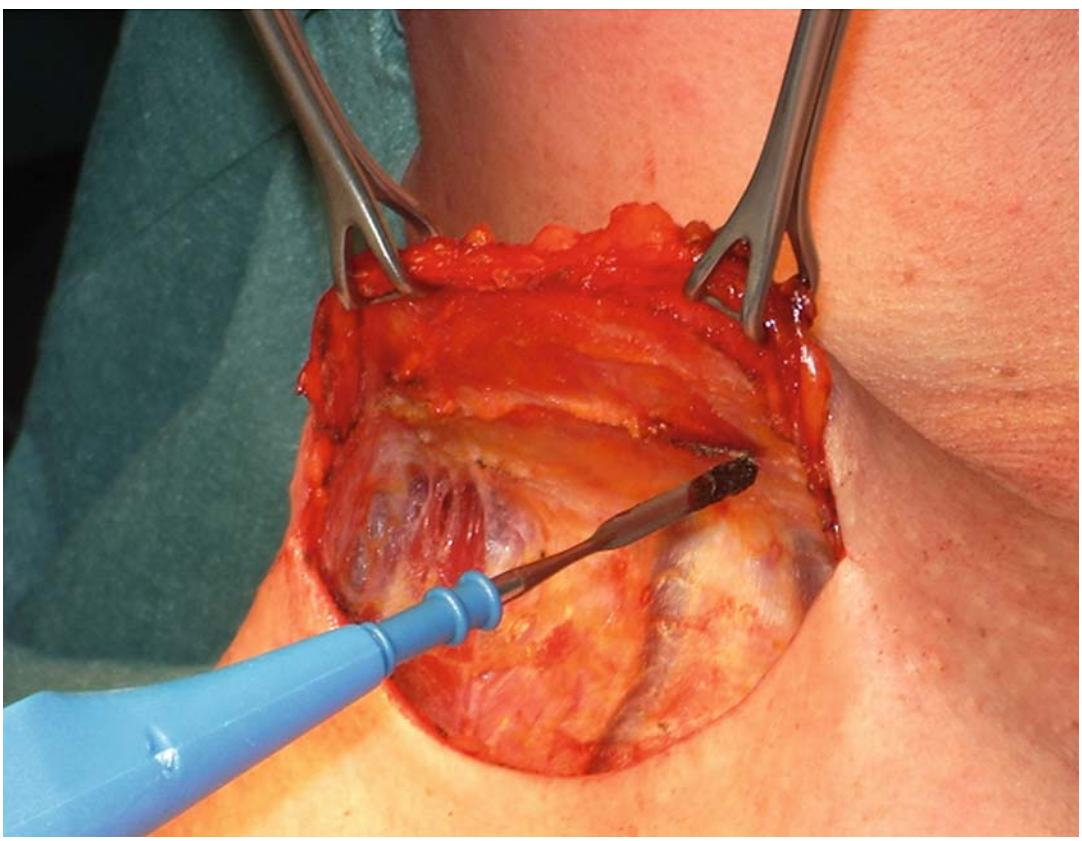

Fig. 12.1. Mobilization of superior flap preserving the anterior jugular veins.

and divided. Division of the strap muscles is rarely necessary in case of very large goiter or in reoperative cases.

Upper Pole

Lateral retraction using forceps allows the opening of the space between the lobe and the cricothyroid muscle, thus often exposing the external branch of the superior laryngeal nerve [5–7]. The external branch of the superior laryngeal innervates the cricothyroid muscle, the action of which is to increase the tension of the vocal cords. Injury can lead to an inability to achieve high notes during singing or speaking. Furthermore, in about 15% of patients, the nerve accompanies the superior thyroid artery. The best way to avoid injury of this nerve is to open the space between thyroid lobe and cricothyroid muscle, to stay lateral to this muscle and to ligate and divide only the superior thyroid artery branches (see Fig. 12.2).

The complete division of the superior vessels enables the surgeon to medially rotate and anteriorly mobilize the gland, which results in optimal exposure of superior parathyroid gland and RLN. In some cases, the posterior branch of the superior thyroid artery can be preserved for superior parathyroid gland supply.

Lower Pole

The inferior thyroid veins can be safely ligated and the trachea observed, allowing a better medial rotation of the lobe with a better exposure of the hilum of the gland.

Lateral Dissection

Lateral retraction of the carotid sheath and medial rotation of the thyroid lobe allows tension of the inferior thyroid artery and makes the RLN easier to identify, most often crossing under or occasionally over the inferior thyroid artery. At this step, RLN must be identified. A small vessel, the vasonervorum, is always observed on this nerve, confirming identification.

Dissection should be meticulous, with the aim of preserving as much of the inferior thyroid artery and its branches as possible, since it supplies the blood to the two parathyroid glands. Truncal ligation of inferior thyroid artery results most often in parathyroid necrosis and should not be done.

Dissection is carried out between the thyroid capsule and the last branches of the inferior thyroid artery [8, 9]. The branches are ligated or clipped individually directly on the surface of the thyroid gland. Dissection is continued from the bottom to the top, preserving parathyroid glands with their blood supply and RLN (see Fig. 12.3).

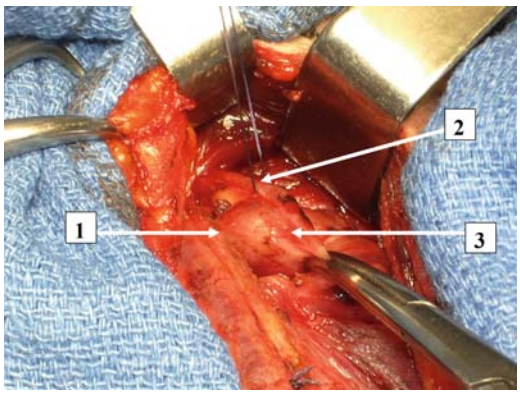

Fig. 12.2. Dissection of the upper pole. Elective division of the superior thyroid artery. (1) Inter crico-thyroid space; (2) superior thyroid artery; and (3), left upper pole of the thyroid.

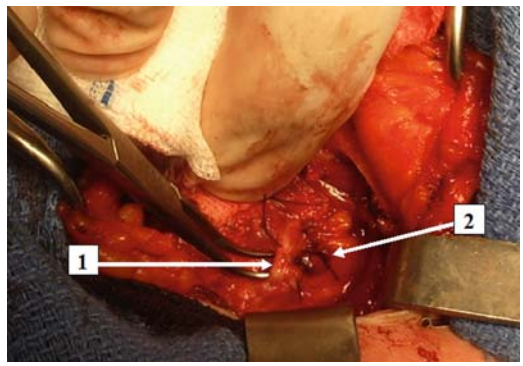

Fig. 12.3. Left superior parathyroid gland. (1) Left recurrent laryngeal nerve and (2) left superior parathyroid gland.

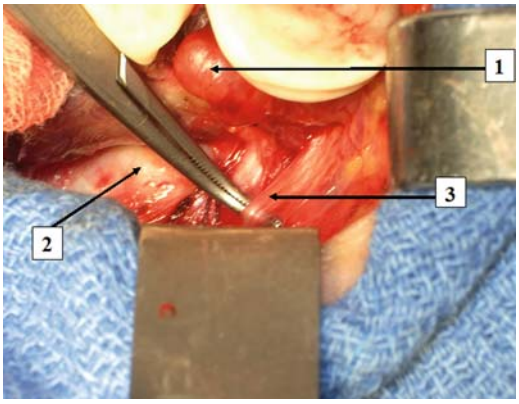

Fig. 12.4. Left Berry ligament dissection. (1) Left thyroid lobe; (2) trachea; and (3) left recurrent laryngeal nerve.

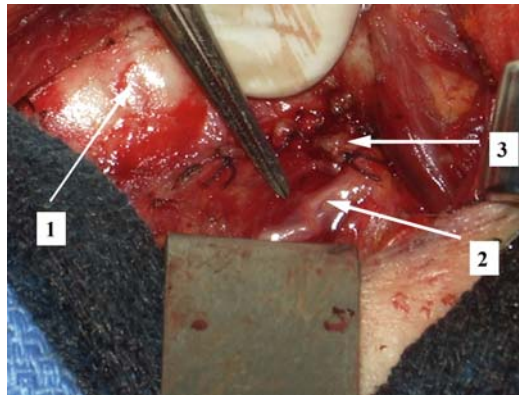

Fig. 12.6. View after left thyroid lobe resection. (1) Trachea; (2) left recurrent laryngeal nerve; and (3) left superior parathyroid gland.

At the upper part of the dissection, the RLN is very close to the thyroid at the site of the ligament of Berry, just before the nerve enters to the cricoid muscle. It is at this site of the ligament of Berry that the RLN is the most vulnerable to injury [10] (see Fig. 12.4). The ligament of Berry is a dense group of vessels and connective tissue that attaches the thyroid to the trachea. Small vessels are often situated in it, posterior to the nerve and bleeding is particularly dangerous in this site (see Fig. 12.5). Positive identification of the nerve must be made prior to ligature. The use of any cautery or other thermal dissection device should be avoided at this step due to the potential for thermal injury of the RLN, which is in close proximity (see Fig. 12.6).

After this step, the thyroid lobe may be quickly dissected free from the trachea. Near the midline, one should look for a pyramidal lobe, which is present in about 80% of individuals and should be removed with the thyroid lobe.

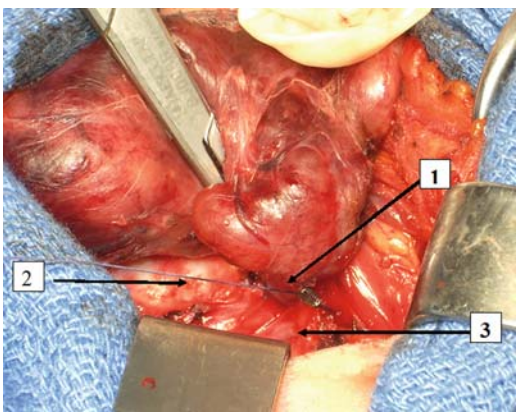

Fig. 12.5. Left Berry ligament dissection. (1) Insertion of posterior part of left thyroid lobe at the Berry ligament; (2), trachea; and (3) left recurrent laryngeal nerve.

Parathyroid Autotransplantation

Even in unilateral lobectomy, all identified parathyroid tissue should be preserved on its native blood supply. If a gland is devascularized during dissection, it should be transplanted [11]. Furthermore, it is sometimes impossible to preserve a parathyroid gland since it is under the thyroid capsulae.

It is recommended to systematically look at the parathyroid glands at the end of operation before closure. The gland can be congestive because of lack of veinous drainage. In this case, the parathyroid capsulae must be incised, and in a few seconds, the gland will recover a nice color.

Sometimes the gland is devascularized and autotransplantation is necessary. In this case, the gland is removed and cut into tiny cubes that are about 1 mm^3 in volume. A pocket is created by separating the muscle fibers of the sternocleidothyroid muscle, avoiding any bleeding. It is important to avoid bleeding since hematoma formation could compromise

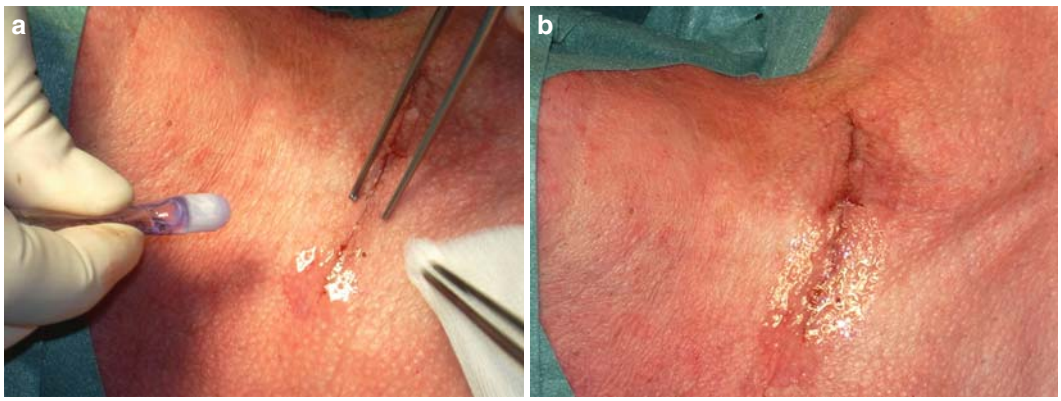

Fig. 12.7. (**a** and **b**) Closure.

the parathyroid function of the graft. The minced tissue is then transplanted into the pocket, which is closed by titanium clip or non-absorbable suture as landmark.

Wound Closure

A drain is necessary only if a very large goiter has been removed with a large persisting space and can never replace accurate hemostasis. It is of little or no use if severe postoperative bleeding occurs [12, 13].

The sternothyroid and sternohyoid muscles are sutured on the midline, as the platysma with 4-0 absorbable suture. The skin is closed by an intradermal 5-0 absorbable suture. In addition, glue can also be used on the skin (see Fig. 12.7).

Reoperative Thyroid Surgery

The best approach is the identification of RLN in a previously undissected area.

A lateral or "back door" approach is recommended in case of reoperation. After standard collar incision, the anterior border of the sternocleidomastoid muscle is mobilized and retracted laterally to expose sternohyoid and sternothyroid muscles. The lateral border of the sternothyroid muscle, inferior to the omohyoid muscle, is mobilized off of the carotid artery and jugular vein. With a retractor, the sternothyroid muscle is reflected medially and the carotid artery laterally. The soft tissue at the inferolateral part of the thyroid lobe is exposed and can be dissected. Dissection is performed in a straightforward manner with, first, identification of the RLN, then control of inferior pedicle, and then superior pedicle.

A second approach is to enter the thyroid bed similarly to the initial operation. Then one can choose either an inferior approach and search for the RLN in the paratracheal region inferior to the area of previous dissection or a superior approach to identify the RLN where it enters the larynx.

Substernal Goiter

Most intrathoracic goiters can be removed though a standard collar incision. A sternotomy is required in less than 10% of cases. In case of bilateral intrathoracic goiter, we recommend commencing the resection on the smaller side and in some cases dividing the isthmus. For intrathoracic goiter, we prefer the toboggan technique described by Charles Proye: the goiter should be mobilized from top to bottom. The first step is to divide and ligate the superior thyroid artery and veins with preservation of the superior parathyroid gland. Section of the head of the sternocleidomastoid muscle or of the straps muscles (sternothyroid or sternohyoid muscles) may help in some cases. The second step is to control middle thyroid veins and mobilise the lateral part of the lobe. It is necessary to identify the position of the RLN before trying to mobilize the intrathoracic part of the lobe. It is often easier to identify the nerve

close to the inferior horn of the thyroid cartilage where it enters the larynx and then to follow it caudally. The pedicle posterior to the nerve can then be controlled, and a space of dissection opened between the nerve and the posterior part of the thyroid. A finger is placed in cervicothoracic space, following the posterior part of the lobe. During this dissection, it is possible to control the location of the nerve in relation to the goiter. Adhesions surrounding the lobe are progressively liberated. With gentle traction on the thyroid lobe, to avoid fragmentation of the thyroid, it is progressively exteriorized with control of the inferior thyroid vessels. When the entire lobe is extracted, it is important to check the absence of the inferior parathyroid gland at the posterolateral surface of the lobe. When a parathyroid gland is devascularized, it should be autotransplanted in the sternocleidomastoid muscle before the end of the procedure. The insertion of a closed suction drain is recommended because of the large remaining mediastinal cavity.

Local or Regional Anesthesia

Local or regional anesthesia represents a safe alternative to general anesthesia in patients with amiodarone-induced thyrotoxicosis [14]. A regional C2-C4 superficial cervical and local field block is performed using a mixture of 0.5% lidocaine and 0.25% bupivacaine. To avoid excessive traction on the muscles, the skin incision is higher on the neck, just inferior to the cricoid cartilage prominence.

Intraoperative Neuromonitoring

In the literature, it is well demonstrated that identification of the RLN reduces the incidence of nerve palsy [15–17]. The principle of neuromonitoring is based on instrumental testing of the reflex arc between the RLN or the vagus nerve and the vocalis muscle. The stimulating electrode is inserted in the vocalis muscle directly or placed at the surface of an endotracheal tube. To ensure the correct response, exact placement of the tube is necessary and no repetitive administration of curare after the initial intubation dose is recommended [17]. During the dissection, either the RLN or vagus nerve should be stimulated. A positive acoustic signal after stimulation of both the vagus nerve and the RLN is an indication that the nerve conduction between the place of stimulation and the vocalis muscle is intact, so the vocal fold function is intact. If there is a positive signal after stimulation of only the RLN and not the vagus nerve, it means that there is usually a RLN paresis with a lesion distally located to the stimulation site.

However, neuromonitoring detects only neurogenic causes of RLN palsy and cannot predict a palsy induced by postoperative hematoma or edema. Multicentric studies have demonstrated lower rates of transient and permanent RLN palsy rates in comparison with conventional RLN identification [15–17]. The learning curve for an optimal use of this technique is estimated to 100 operations.

Minimally Invasive Thyroidectomy

Endoscopic neck surgery was first described for parathyroidectomy by Gagner in 1996 [18], and subsequently proposed for thyroid surgery. Four techniques are currently performed: two complete endoscopic techniques and two video-assisted techniques. These techniques are safe and reproducible but indicated only in selected patients (see Table 12.1).

Table 12.1. Relative indications of minimal invasive thyroidectomy

Indications	Absolute contraindications	Relative contraindications
Nodule <3 cm of diameter	Previous neck surgery	Previous neck irradiation
Thyroid estimated volume <20 mL	Large goiter	Hyperthyroidism
Benign or low-grade follicular lesion	Locally advanced cancer	Thyroiditis
Low-risk papillary carcinoma	Lymph node metastases	

Complete Endoscopic Thyroidectomy

Gagner Technique

The patient under general endotracheal anesthesia is placed in the supine position with neck hyperextension. A 5-mm horizontal incision is performed above the sternal notch. The cervical fascia is opened and the space below the platysma is developed. A 5-mm trocar is inserted into the subplatysmal space and secured with a purse string suture. Pressure insufflation is limited to 10 mm Hg. Initial dissection along the anteromedial border of the ipsilateral sternocleidomastoid muscle (SCM) is performed by advancing a 0° endoscope. Once an adequate avascular space has been created, a 30° endoscope is used. Additional trocars are inserted under direct vision: a 2- to 3-mm trocar at the midline, a 2- to 3-mm trocar at the midportion of the ipsilateral SCM, and a 5- to 10-mm trocar along the anterior border of the SCM. The sternohyoid and sternothyroid muscles are retracted anteromedially after opening the linea alba with the hook. The thyroid lobe is mobilized without using cautery in the deeper tissue planes. The middle thyroid vein is ligated using 5-mm clips or the 5-mm harmonic scalpel. The RLN and the parathyroid glands are identified and carefully dissected from the thyroid gland. The inferior thyroid artery is identified, ligated with 5-mm clips as close as possible to the thyroid gland, and divided with the RLN in full view. The superior pole vessels are isolated, clipped, and divided when the superior laryngeal nerve has been identified. The inferior pole vessels are divided with the harmonic scalpel. The Berry's ligament is divided with the harmonic scalpel after releasing the anteromedial attachments of the RLN. The specimen is then placed in a small bag (thumb portion of a surgical glove) and extracted through the superolateral trocar site. The skin is closed with adhesive strips [19, 20].

Cougard Technique

This technique is a variant of Gagner technique with central approach, which allows a bilateral exploration of the neck with three trocars. The patient is in the supine position with hyperextension of the neck. A 1.5-cm horizontal incision is made above the sternal notch. The cervical fascia is opened and the linea alba is divided. A space between superficial and deep strap muscles is developed. A 5-mm trocar is inserted into the subplatysmal space and secured with a purse string suture. Pressure insufflation is limited to 8 mm Hg. A 0° 5-mm endoscope is inserted. A working space is created with the camera. One 3-mm trocar is inserted under direct vision, to avoid anterior jugular veins, on the left side and a 5-mm trocar on the right side. The sternohyoid and sternothyroid muscles are retracted anteromedially. After mobilization of the thyroid lobe, the inferior thyroid veins are first ligated by clips or 5-mm harmonic scalpel and divided, followed by the middle thyroid vein. The superior pole vessels are isolated after identification of the superior laryngeal nerve and ligated. The inferior thyroid artery is isolated and ligated after identification and preservation of the RLN and the parathyroid glands. Isthmus is divided using harmonic scalpel and extracted by midline incision. The incisions are closed with surgical glue [21].

Video-Assisted Technique (MIVAT)

Lateral Approach: Henry Technique

The patient is in a supine position without hyperextension of the neck to avoid traction of the SCM and strap muscles. A 12- to 15-mm a transverse neck incision is made just above the isthmus. The anterior border of the SCM is liberated from the cervical fascia and the thyroid lobe to the carotid sheath up to the prevertebral fascia. The superior limit of the dissection is the omohyoid muscle. To enlarge the space of dissection, a moist swab is stuffed upward and downward. Two 2.5-mm ports are inserted on the line of the anterior border of the SCM, 6 cm above and 3–4 cm below the first skin incision. These are inserted by passing a sharp trocar under direct vision, (from in to out) via the initial incision and then using this trocar as a guide stick to insert the working ports (from out to in). Then a 10-mm trocar is inserted through the incision. Pressure insufflation is limited to 8 mm Hg. All dissection is performed with 10-mm 0° endoscope and 2-mm graspers and scissors. The dissection starts with the identification of anatomic structures, particularly the RLN. The thyroid lobe is mobilized. Small vessels are cauterized. The branch of the inferior thyroid artery is isolated but not ligated. The

branch of the superior thyroid artery is also isolated with identification of the external branch of the superior laryngeal nerve. The superior parathyroid gland is dissected from the thyroid lobe. The inferior pole vessels are isolated with preservation of the inferior parathyroid gland. Then the dissection is performed medially to separate the thyroid lobe from the sternothyroid muscle up to the isthmus. The endoscopic dissection is finished with the removal of the three trocars. All vessels are ligated and divided with harmonic scalpel through the skin incision. The thyroid lobe is extracted and the isthmus divided with harmonic scalpel. There is no traction on the RLN during this step. Only the platysma is sutured and the skin is closed by skin sealant [22–25].

Central Approach: Miccoli Technique

With this technique, the patient is also in supine position without neck hyperextension. A 15-mm horizontal incision is performed 2 cm above the sternal notch. After dissection of the subcutaneous fat and platysma, the cervical linea alba is divided longitudinally for 3 cm. A small retractor is used to retract the strap muscles and another one for the thyroid lobe, which is gently dissected from the strap muscles. The two retractors maintain the operative space, and a 30° 5-mm endoscope is inserted. Dissection of the thyrotracheal groove is completed by 2-mm instruments inserted also through the single skin incision. The middle vein is ligated by 3-mm vascular clips to avoid electrocautery. The upper pedicle is then exposed with downward retraction of the thyroid. The upper vessels are selectively ligated by clips and cut after identification of the external branch of the superior laryngeal nerve in most cases. Inferior vessels are also clipped and cut. After lifting up the thyroid lobe, the fascia is opened. Small vessels are closed by clips and the RLN and the parathyroid glands are dissected from the thyroid. Endoscope and the retractors can then be removed. The thyroid lobe is gently extracted and remaining vessels and Berry's ligament are ligated and cut. The laryngeal nerve is checked before division of the isthmus. After control of hemostasis, the linea alba and platysma are sutured with reabsorbable suture. The skin is closed by skin sealant or subcuticular suture [23, 25].

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13

Lymph Node Dissection in Thyroid Cancer

Henning Dralle and Andreas Machens

Introduction

In locally advanced thyroid cancer confined to the neck, lymph node surgery pursues curative intentions but is also performed for the prevention of complications. These complication may arise from the invasion of local structures, such as recurrent laryngeal nerve, compromising quality of life, or trachea and esophagus, which may be life-threatening [1]. The tumor biology of thyroid cancer is mainly determined by the respective tumor type (papillary, follicular, low-differentiated, undifferentiated, and medullary) and the extent of disease (intrathyroidal growth versus extrathyroidal extension; locoregional versus distant metastases). To complicate the matter further, clinical outcome is also influenced by a host of proliferative factors.

Surgery is the single most important, potentially curative treatment modality not only for the primary tumor but also for locoregional node metastases. Radioiodine treatment in differentiated thyroid cancer and external beam radiation in locally advanced differentiated or undifferentiated thyroid cancer may complement but not replace surgery. For distant metastases, surgical intervention is rarely indicated, and if so, only as one component of a multimodal approach [2–5]. Such rare instances include solitary and localized distant metastases, which can be removed safely with acceptable surgical morbidity.

Because thyroid cancer is uncommon and often takes a chronic course over decades, management recommendations [6–8] are exclusively derived from single-center or multi-institutional experience [9, 10]. Mimicking clinical reality [11, 12], there is only one intervention but no head-to-head comparison of different types of treatment which would facilitate evidence-based decisions tailored to the needs of individual patients. This weak evidence base is a frequent source of disagreement. There is no consensus about the indication for, and extent of, lymph node dissection (LND) (routine versus therapeutic; selective versus compartment-oriented). As a result, recommendations are based on indirect inferences, personal experience, or just eminence instead of evidence [13].

Locoregional Lymph Nodes: Surgical Anatomy and Classification Systems

The prognostic relevance of lymph node metastases has remained controversial in solid cancers, especially in thyroid cancer. As in most types of solid cancer, including thyroid cancer, the frequency of locoregional lymph node metastases increases with tumor size [14]. There is also evidence of a direct relationship between the number of locoregional node

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metastases and the frequency of distant metastases, which is not understood fully. Distant metastasis, the strongest indicator of cancer-specific death, sometimes occurs in the absence of lymph node metastases [15, 16]. Several issues regarding the pathobiology and clinical implications of lymphatic spread in thyroid cancer remain unsettled. These areas of uncertainty concern the incidence and prognostic importance of skip metastases [17] and the anatomical boundaries between the "locoregional" and the "distant" type of lymph node metastases [18]. Disregarding tumor biology, the current concepts of surgical anatomy and classification systems rest wholly on the histopathological involvement of locoregional nodes in surgical specimens.

In solid cancer, removal of locoregional lymph node metastases can result in cure. The ability of closely reflecting lymphatic spread is the key requirement for any classification system of locoregional lymph nodes. Specifically devised for thyroid cancer, the compartment classification seems to meet this requirement better than any other classification system, which are more specific for head and neck tumors. This classification system defines three neck compartments and one mediastinal compartment which contain all the respective locoregional nodes embedded in fibrofatty tissue. [19–25]. Representing the first echelon of locoregional node metastasis, the central neck compartment can be conceived clinically as the "epicenter" of lymphatic spread in thyroid cancer. The central neck compartment is separated from the lateral neck compartments by the medial border of the common carotid artery [22, 26], and from the upper mediastinal (infrabrachiocephalic) compartment through a virtual line drawn through the origin of the right and left common carotid arteries from the aortic arch. Anatomically, the mediastinal compartment comprises only those nodes located below this virtual line. To remove all mediastinal nodes falling under this anatomical definition, a transsternal approach is always required. Less well defined are the external lateral borders of the lateral neck and mediastinal compartments. There are no fasciae or major vessels to serve as anatomical landmarks between lateral cervical and nuchal nodes, or between upper mediastinal and middle mediastinal nodes.

Unfortunately, no standard classification of locoregional lymph nodes exists for thyroid cancer. At least four competing staging systems are in use (Fig. 13.1):

1. The American Academy of Otolaryngology – Head and Neck Surgery Dissection Classification [26, 27] describing six different levels in the central (level Ia, Ib, and VI) and lateral (IIb, IIa, III, IV, Va, Vb) neck, but excluding the infrabrachiocephalic upper mediastinum;
2. The Japanese Society of Thyroid Surgery Classification [25] describing seven lymph node groups in the central (I–IV) and lateral (V–VII) neck, but excluding the infrabrachiocephalic upper mediastinum;
3. The International Union Against Cancer (UICC) classification [28] describing eight lymph node groups in the central [1, 2, 8] and lateral [2–7] neck, but also excluding the upper mediastinum; and
4. The Compartment Classification [22–24, 29, 30] describing four locoregional compartments in the neck (C1, C2, C3) and upper mediastinum (C4).

From a practical point of view, all four classification systems have limitations and are incompatible with one another. The compartment classification is the most straightforward classification system because it (i) uses the major arterial structures in the neck and mediastinum as anatomical landmarks; (ii) affords differentiation by side; and (iii) includes the upper mediastinum.

The number of lymph nodes removed from the respective regions depends not only on the extent of node metastasis and the surgical technique of LND but also on the diligence with which the histopathological analysis is carried out. On average, the central neck compartment harbors 10 nodes (five nodes on either side), the lateral neck compartments 20 nodes each, and the mediastinal compartment 10 nodes (five nodes on either side) [30, 31]. Although the UICC classification uses the number of positive nodes as a prognostic marker for many solid cancers, including breast carcinoma [28], the UICC classification for thyroid cancer does not capture this important piece of information. Recent literature reports suggest that the presence of more than 10 lymph node metastases is linked to a worse outcome in patients with

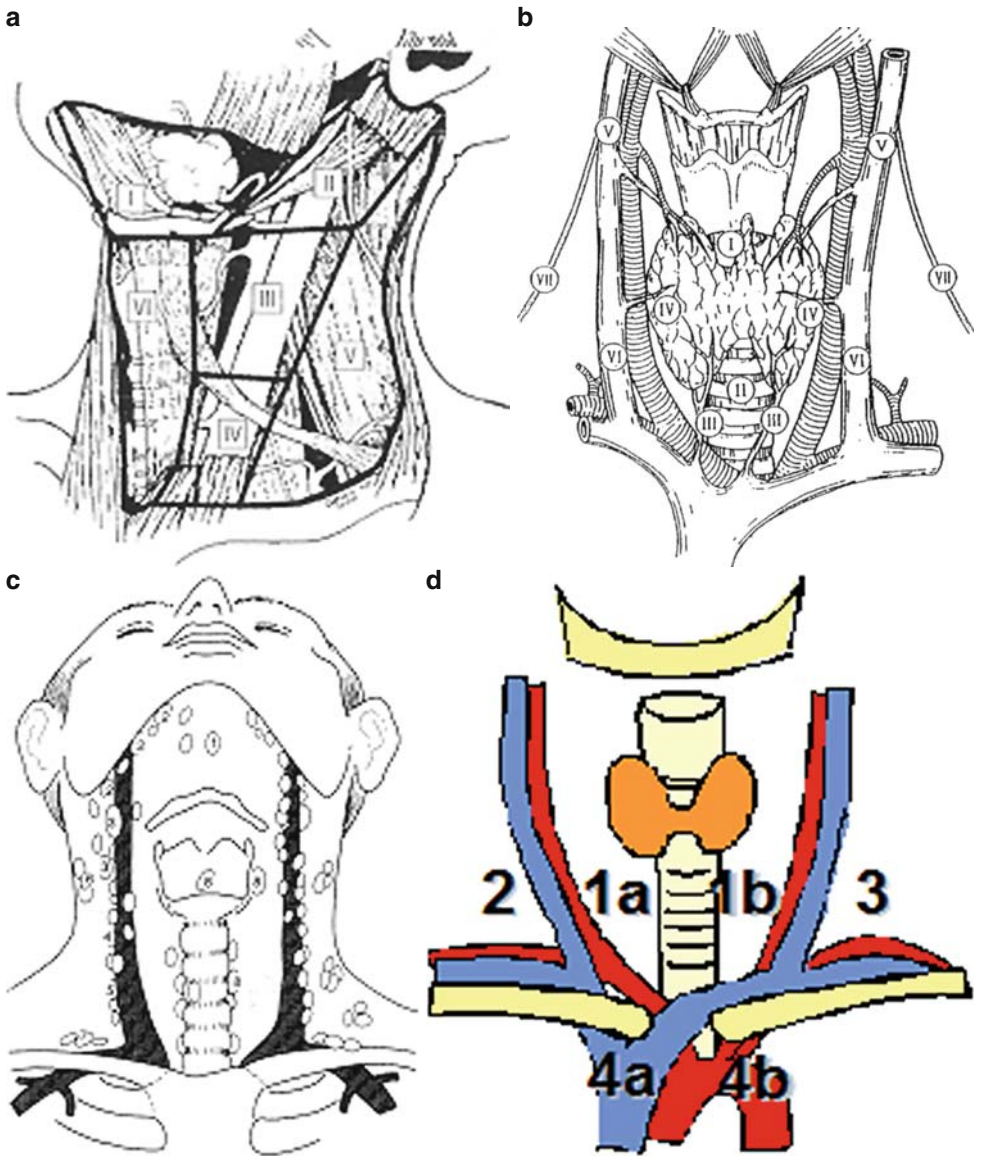

Fig. 13.1. Classification systems of locoregional lymph nodes and lymph node groups. (**A**) American Academy of Otolaryngology – Head and Neck Surgery (ACOLHNS): (I) submental (IA) and submandibular (IB); II, upper jugular (IIA, IIB); (III) middle jugular; (IV) lower jugular; (V) posterior triangle (VA, VB); (VI) anterior (reprinted from Robbins KT, Clayman G, Levine PA, Medina J, Sessions R, Shaha A, Som P, Wolf GT and the Committee for Head and Neck Surgery and Oncology, American Academy of Otolaryngology-Head and Neck Surgery. Neck dissection classification update. Arch Otolaryngol Head Neck Surg 2002; 128: Fig. 1, p. 752). (**B**) Japanese Society of Thyroid Surgery (JSTS): (I) prelaryngeal; (II) pretracheal; (III) paratracheal; (IV) paraglandular; (V) deep upper cervical; (VI) deep lower cervical; (VII) deep lateral cervical (reprinted from Surgery, vol. 131, Qubain SW, Nakano S, Baba M, Takao S, Aikou T. Distribution of lymph node micrometastasis in pN0 well-differentiated thyroid carcinoma, pp. 249–56, copyright 2002, with permission from Elsevier). (**C**) International Union Against Cancer (UICC): (1) submental; (2) submandibular; (3) cranial jugular; (4) medial jugular; (5) caudal jugular; (6) dorsal cervical along accessory nerve; (7) supraclavicular; (8) prelaryngeal and paratracheal (reprinted with permission from Wittekind Ch. Greene FL, Henson DE, Hutter RVP, Sobin LH. TNM Supplement. 3rd ed. Wiley-Liss New York, 2003, Fig 2a, p. 27). (**D**) Compartment Classification of Thyroid Locoregional Nodes (CC): (1) cervicocentral right (1a) and left (1b); (2) cervicolateral right; (3) cervicolateral left; (4) upper mediastinal right (4a) and left (4b).

papillary and medullary thyroid carcinoma (MTC) [32–34]. For follicular, poorly differentiated, and undifferentiated carcinoma, there are no pertinent data.

Indications for Lymph Node Dissection

Lymph node dissection is performed with curative (elective or prophylactic versus therapeutic) or palliative intent. Its clinical importance is commensurate with the intensity of lymphatic tumor dissemination, which is higher in papillary thyroid cancer (PTC) and MTC than in other thyroid cancers. Because of the chronic course of the disease and the threat of invasion of the neck from extranodal tumor growth [35], palliative LND has a prominent role within the treatment concept for PTC and MTC.

With increasing resolution, imaging has increased in importance, laying out a roadmap of positive locoregional nodes, not only in recurrent but also in primary thyroid cancer. Advances in cervical ultrasonography, such as the development of high-resolution imaging systems and the Doppler power mode, have improved the detection of suspect nodes based on a combination of anatomical and functional parameters. These substantial improvements in imaging have had major repercussions on the concept of stage-oriented surgery, enabling a more tailored approach in planning LND to the extent of lymph node metastases. In recurrent thyroid cancer, this progress has enhanced the effectiveness of reoperations in the neck [36–44]. The new technology of fluoro-deoxyglucose (FDG)-PET fusion has further refined the localization of residual tumor and improved the projection of outcome in radioiodine-negative differentiated [45–49] and MTC [50, 51]. A recent study on 400 thyroid cancer patients found a negative correlation between FDG avidity and cancer-specific survival [49]. As a consequence of these developments, invasive localizing techniques for occult thyroid cancer, such as selective venous catheterization, have largely been abandoned [52, 53].

Papillary Thyroid Carcinoma

When one considers the recent results of large single-center studies and systematic evidence-based analyses, there is no doubt that a clinical diagnosis of node metastases reflects more aggressive tumor biology in papillary thyroid carcinoma (PTC) [54, 55] with a higher risk of locoregional and distant recurrence [15, 33, 56–59]. While therapeutic LND is unanimously accepted, there is still an ongoing debate regarding the clinical relevance of occult node metastases and the need for routine (i.e., prophylactic) LND of the central [43, 59, 60–62] and lateral [39, 40, 41, 63] neck compartments.

For papillary microcarcinoma, where lymph node metastases do occur, there are no data to support the use of routine central or lateral node dissection [39, 43, 60, 62] (Table 13.1). For gross PTC (>10 mm in diameter), conversely, there is mounting evidence that routine central node dissection should be performed as a minimum [34, 61, 66]. Central LND has been connected to higher rates of transient and sometimes permanent hypoparathyroidism and recurrent laryngeal nerve palsy [61, 62, 64–67]. This risk of surgical morbidity, which is quite low in experienced hands, must be balanced with the high recurrence rates after total thyroidectomy alone, and the much higher complication rates after completion central neck dissection. All in all, these data argue in favor of routine central node dissection for PTC measuring >10 mm in diameter.

Lateral cervical and, even more, transsternal mediastinal node dissection are a different matter, not only because the potential for surgical morbidity is much higher, but also cosmetically because the skin incision needs to be significantly enlarged to gain full exposure [22, 68, 69]. During total thyroidectomy for PTC, regardless of the need for central LND, the lateral compartments are not routinely exposed. Therefore, it seems prudent to restrict routine lateral neck dissection to those tumors with risk factors of lymphatic spread, such as large primary tumors and those with massive extrathyroidal extension [58]. In PTC, transsternal LND is rarely indicated in the infrabrachiocephalic upper mediastinum, but clearly is required for confirmed node metastases [22, 70].

Table 13.1. Involvement of central and lateral compartments in PTC ≤10 mm versus >10 mm

	Maximum primary tumor diameter							
	≤10 mm				>10 mm			
	Central		Lateral		Central		Lateral	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral
First surgery (%) ($n = 31$)	14	7	29	0	41	18	29	6
Reoperative surgery (%) ($n = 101$)	19	5	5	–	38	18	25	10

Source: Adapted from Machens A, Hinze R, Thomusch O, Dralle H. Pattern of nodal metastasis for primary and reoperative thyroid cancer. World J Surg. 2002;26:22–28. Reprinted with kind permission of Springer Science and Business Media.

Lateral node metastases located contralateral in relation to the primary tumor are a well-known event in head and neck cancer [71] but are quite rare in well-differentiated PTC (Table 13.1). Some PTC variants, such as the diffuse sclerosing variant, may coincide with Hashimoto's thyroiditis and often reveal involvement of both thyroid lobes and lateral node metastases in both the right and left neck [72–76]. When lateral lymph node metastases are detected in the contralateral neck of previously untreated patients, routine dissection of the central and both lateral neck compartments is justified.

Follicular Thyroid Carcinoma

Survival following well-differentiated follicular thyroid cancer is mainly determined by the presence of distant metastases [77–82]. Distant metastases are found in some 20% of patients, as opposed to some 6% in PTC [16]. With the growth of the primary tumor, lymph node metastases occur more frequently. The size threshold for lymph node metastases is higher in follicular thyroid carcinoma (FTC) (>20 mm) than in PTC (<10 mm) [16]. In FTC, but not PTC, node metastases are associated with distant metastases, carrying a much worse prognosis [15]. Because of this fact, most authors found no evidence that node metastases in FTC have an independent adverse effect on survival [83]. Unlike therapeutic LND for preemption of extranodal growth and subsequent invasion of the neck, there is no indication for routine LND in FTC. The same surgical strategy applies to the oxyphilic ("Hürthle cell") variant of FTC because the rates of lymph node and distant metastasis are similar to those for nonoxyphilic FTC [84].

Poorly Differentiated Thyroid Carcinoma

The 6th edition of the WHO classification of thyroid malignancies, which appeared in 2002 [85], reclassified thyroid carcinomas with limited evidence of follicular cell origin as poorly differentiated thyroid carcinomas (PDTCs). Both morphologically and biologically, these poorly differentiated tumors take an intermediate position between differentiated and undifferentiated (anaplastic) thyroid carcinomas (UTCs) [86–92].

Lymph node metastases and distant metastases occur more frequently (45–65%) [89, 91] in poorly differentiated than in well-differentiated thyroid carcinoma. [86, 91]. In one study [89], up to 70% of distant metastases concentrated radioiodine. Established prognostic factors include primary tumor size, extrathyroidal extension, and distant metastases but not lymph node metastases [86, 89, 91].

By definition, PDTC may originate from FTC or PTC. Except for large extrathyroidal PDTC, the preliminary data do not support routine LND.

Undifferentiated (Anaplastic) Thyroid Carcinoma

Extrathyroidal extension with tracheal invasion and rapid progression to tracheal obstruction with a high prevalence of distant metastasis are the hallmarks of UTC. Despite being quite common (30–40%) [93], lymph node metastases are not a key component of surgical treatment unless the completeness of the resection hinges on the removal of these nodes [94–98]. There is no consensus whether complete resection prolongs survival in UTC [99]. Because of this fact, extensive surgery with special emphasis on the preservation of organ function, supported by adjuvant external radiotherapy, with or without adjuvant chemotherapy, constitutes the current treatment of choice for UTC [93, 94, 96, 97, 100–104]. LND is one means of achieving local control, without having a measurable effect on survival.

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma, or C-cell carcinoma, is a unique tumor entity within the spectrum of thyroid cancer. Originating from neural crest cells, it differs in many ways from other thyroid cancers. Unlike follicular cell-derived thyroid cancers, MTC cells are unable to express the sodium/iodine symporter and hence do not concentrate iodine. As a tribute to their neuroendocrine heritage, MTC cells synthesize and secrete various hormonal peptides, including calcitonin and carcinoembryonic antigen (CEA), which can be used as tumor markers. By the time of diagnosis, up to 20% of patients have developed distant metastases [105]. Even with extensive LND, only 60% of node-negative and 10% of node-positive patients are cured [105]. Despite these facts, overall survival rates in MTC are remarkably good and do not differ much from those seen in differentiated thyroid cancer [106]: 89% at 5 years [107] and 75–85% at 10 years [108, 109]. Far from being a homogeneous entity, MTC encompasses a wide range of tumors from rather indolent [110] to highly aggressive [1, 111]. Because calcitonin-secreting C-cells are highly sensitive to external stimulation, calcitonin levels are very useful for early MTC screening but tend to fluctuate on repeated measurements. For long-term monitoring of advanced disease, serum CEA levels may be more useful because they tend to be more stable [105, 112, 113].

Lymph node metastases have a prominent role in MTC [105, 114, 115]. Owing to their high prevalence, enlarged nodes may be the first clinical evidence of disease. As early as 1968, just 7 years after MTC was recognized as a separate tumor entity, Woolner et al. [116] described the prognostic importance of lymph node metastases in 77 MTC patients: Node-negative patients had a life expectancy similar to the general population whereas node-positive patients had a 10-year survival rate of just 42%. Second only to distant metastases, lymph node metastases are a measure of systemic disease. Furthermore, lymph node metastases can give rise to locoregional recurrence, necessitating the removal of all positive nodes.

Incorporating recent evidence and drawing on personal experience, the indication for, and the extent of, lymph node surgery can be summarized as follows:

1. Lymph node metastases may occur with primary tumors as small as 5 mm. The surgical window of cure between the development of lymph node metastases and distant metastases can be quite narrow because distant metastases have been found with 10 mm small primary tumors [105]. These data underscore the need to detect MTC early on before they have grown larger than 10 mm.
2. Central and lateral node metastases on the same side of the neck are found equally often (Table 13.2) [14, 117]. Nevertheless, lymphatic spread is a gradual process which is dependent on the number of positive nodes: with one to three positive central nodes, involvement of the ipsilateral lateral neck increased from 10 to 77%, reaching 98% with four or more positive central nodes [118]. These data suggest that, at the very least, both the central neck compartment and the lateral neck compartment on the side of the primary tumor should be dissected when a single positive node is identified in the central neck.
3. The risk of lateral node metastases in the contralateral neck and the mediastinum increases with the size of the primary tumor [117, 119], with multifocal tumor growth in the thyroid gland [120], and with the number

Table 13.2. Involvement of central, lateral, and mediastinal compartments in MTC ≤10 mm versus >10 mm

	Maximum primary tumor diameter									
	≤10 mm					>10 mm				
	Central		Lateral			Central		Lateral		
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Mediastinal	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Mediastinal
First surgery (%) ($n = 68$)	14	3	11	0	0	46	39	58	33	27
Reoperative surgery (%) ($n = 93$)	56	19	50	19	0	60	31	49	22	23

Source: Adapted from Machens A, Hinze R, Thomusch O, Dralle H. Pattern of nodal metastasis for primary and reoperative thyroid cancer. World J Surg. 2002;26:22–28. Reprinted with kind permission of Springer Science and Business Media.

of central node metastases in the neck. With one to nine positive nodes in the central compartment, contralateral lateral neck involvement increased from 5 to 38 %, reaching 77% with 10 or more positive central nodes [121]. For patients with intensive central neck involvement, microdissection of the central and both lateral neck compartments is recommended.

4. Lymph node metastases have not been observed in the infrabrachiocephalic upper mediastinum with small primary tumors up to a tumor diameter of 10 mm [14]. Like lateral node metastases in the contralateral neck, mediastinal node metastases also occur at the same time as distant metastases [121, 122]. Because of this coincidence with systemic disease, the clinical benefit of transsternal mediastinal LND, without any evidence of mediastinal disease, is too small to warrant its routine use.
5. Sporadic and hereditary MTC do not differ from each other in metastatic behavior (lymphangic, hematogenous) when they have the same tumor stage [114, 120]. The required extent of dissection is largely determined by oncologic features, such as multiple primary tumors, which are typical of hereditary disease, and neck node metastases, which tend to be more advanced in sporadic disease for which early screening is less cost-effective and less widespread.
6. In hereditary disease, most of which is identified through early screening, the timing of prophylactic thyroidectomy and the extent of lymph node surgery are based more on preoperative calcitonin levels than on any other piece of information including type of RET mutation or preoperative ultrasound findings. The so far largest studies from the Euromen Study Group [123–125], the French GETC Study Group [126], and smaller series from Germany and Austria [127], Halle [128, 129], St. Louis [65], and Houston [130] revealed the critical function of lymph node metastases in achieving cure, which play a far more important role than the primary tumors, the originators of lymphatic dissemination. Especially when they are small, lymph node metastases cannot always be identified, neither by high-resolution cervical ultrasonography nor by visual inspection, direct palpation or frozen section during the operation. In this setting, determination of preoperative basal calcitonin levels is useful to identify those carriers who have not yet developed lymph node metastases. Based on literature data [125, 126] and personal experience, lymph node metastases are not present in gene carriers who still have normal basal calcitonin levels. It is therefore reasonable to perform compartment-oriented LND in previously untreated gene carriers with abnormal basal calcitonin levels but not in those with normal basal calcitonin levels [131].
7. In clinically apparent MTC, systemic disease is common. In occult MTC, laparoscopy [132], bone scintigraphy and MRI [133], liver angiography [134], FDG-PET scanning [50], and selective venous sampling of calcitonin [135] are able to uncover distant metastases as the source of persistent hypercalcitoninemia. In clinical practice, these sophisticated techniques can help one to plan reoperations more adequately, sparing patients with occult MTC an odyssey through many hospital departments with repeated imaging and frequent reoperations.
8. With the introduction of the technique of compartment-oriented microdissection, locoregional reoperations now result more often in the normalization of postoperative calcitonin levels [24, 136–139]. Indicative of surgical cure, this biochemical normalization is widely taken as a measure of surgical success. Because locoregional recurrence frequently acts as the "pacemaker" of disease, even extensive procedures are justified when they provide symptomic relief [111, 119].
9. Despite some improvements in recurrence-free and overall survival, biochemical cure rates remain unsatisfactory, especially for node-positive MTC patients (10–20%). Locoregional lymph node metastases and distant metastases represent the largest obstacle to normalization of serum calcitonin levels. With more than 10 lymph node metastases, and more than two involved compartments, biochemical cure is exceptional due to concomitant distant metastases [32, 117]. Early detection through calcitonin screening and adequate surgery based on the compartment-oriented dissection technique remain decisive factors of cure [140–142].

Surgical Techniques of Lymph Node Dissection

A recent study [143] suggested that as many as 75% of reoperations for persistent or recurrent PTC might have been preventable if the initial operation had followed applicable practice guidelines. Root cause analysis revealed that mainly the extent of initial LND had been inadequate, much more often than the extent of thyroid resection which accounted for only 25% of inadequate procedures. Likewise, a significant proportion of patients with gross MTC continue to receive substandard treatment. Based on US SEER data, 15% of MTC patients receive less than total thyroidectomy, and 41% of MTC patients with stage IV disease have no LND whatsoever [144]. Although no comparable data exist for the other types of thyroid cancer, it is reasonable to assume that the failure to adequately dissect cervical lymph nodes is a major cause of locoregional failure in patients with thyroid cancer, prompting even more operations at the cost of additional morbidity.

Significant progress in preoperative work-up and the development of the technique of compartment-oriented microdissection [24, 117, 136, 137, 145–147] have resulted in more adequate initial operations for thyroid cancer. Several techniques of lymph node management are available to address the wide range of node metastasis from low-risk single-node to high-risk multiple-node involvement: sentinel node technique, focused approach, regional LND including excision of single nodes ("berry picking"), and compartment-oriented microdissection.

Sentinel Node Technique

A multitude of studies have appeared over the past decade dealing with the feasibility and accuracy of the sentinel node technique for differentiated thyroid cancer [148–158]. These studies reported a substantial rate of false-positive and, even more often, false-negative results [159, 160]. The high variability of lymphatic drainage in more than one direction and the frequent existence of multiple primary thyroid tumors render the sentinel node approach unsuitable for routine use in patients with thyroid cancer outside a research setting.

Focused Approach

For a carefully selected subset of patients with recurrent thyroid cancer, the focused approach through a small skin incision may be appropriate as a minimum procedure. As in any targeted intervention, the focused approach requires a valid surgical target that must have been identified before or, at the latest, during the operation [161]. Various techniques have been developed to guide the excision of that target, including radioiodine-directed probes [162, 163], hook needles [164], and high-resolution ultrasonography [161, 165, 166]. The latter two techniques also work for recurrent radioiodine-negative differentiated and medullary thyroid cancer. As a matter of principle, a focused approach is not indicated for recurrent thyroid cancer with tumor deposits at multiple sites.

Regional Lymph Node Dissection Including Excision of Single Nodes ("Berry Picking")

Like the focused approach, the excision of single nodes ("berry picking") may be suitable for some patients who previously underwent compartment-oriented LND for low-risk thyroid cancer and now require reoperations for locoregional recurrence in the dissected area. For cosmetic reasons, the neck should preferably be entered through a previous skin incision after excision of the scar. Neither approach is recommended for the initial clearance of positive nodes [167]. As a general rule, gross node metastases from MTC and PTC are surrounded by occult node metastases, all of which can be dispersed across more than one region. If not cleared entirely, they are a frequent source of recurrence. For these reasons, the single-node and single-region approach have been largely abandoned [168].

Compartment-Oriented Microdissection

Compartment-oriented microdissection [24] is the standard procedure for node-positive thyroid cancer. It can involve one or more compartments. While, mainly advocated for surgery

with curative intent, compartment-oriented microdissection can also be effective in maintaining local control in patients with stable systemic disease. Depending on the clinical context, the dissection may progress from the lateral compartment(s) toward the central compartment (centripetal approach) or vice versa (centrifugal approach). Upon preoperative evidence of locally advanced thyroid cancer in a previously untreated patient, the centripetal approach is the procedure of choice at the authors' institution. In the absence of such confirmation, the operation starts at the central neck compartment, which is removed together with the thyroid gland as one contiguous surgical specimen. Upon histopathological confirmation of cancer, the dissection proceeds to the lateral neck compartments, one or both of which are cleared as needed.

As elsewhere in the body, solid organs are embedded in fibrofatty tissue. Containing arteries, veins, and the lymphatic system including the locoregional nodes, this fibrofatty tissue fills the space between these organs. The concept of compartment-oriented microdissection is to dissect the compartmental fatty tissue as one contiguous surgical specimen to ensure that all locoregional nodes are removed whereas vessels, nerves, and muscles (other than strap muscles) are preserved. This way, the compartment-oriented approach provides for the elimination of extranodal tumor deposits from the neck [169, 170].

As outlined above, the central neck compartment is limited dorsally by the trachea with the thyroid gland and laterally by the medial aspect of the common carotid arteries. Anatomical landmarks thus delineate the borders of the central neck compartment. Conversely, no such landmarks exist to mark off the lateral neck and the mediastinal compartment medially from the pharyngeal and laterally from the nuchal, axillary and middle mediastinal nodes, respectively.

The surgical technique of compartment-oriented microdissection in the neck and mediastinum has been described repeatedly in surgical textbooks [171, 172]. The key elements of this technique can be summarized as follows.

Central Neck Compartment

Whenever there is evidence of extrathyroidal extension of thyroid cancer, the strap muscles are removed together with the central lymph node compartment (and the thyroid gland, if not yet resected) as one contiguous surgical specimen. At first surgery, the thyroid gland is removed as a whole together with the right and left portions of the central neck compartment. For oncological reasons, the thyroid gland is not divided at the isthmus, nor is it separated from its adjacent fatty tissue, which encloses the central lymph nodes (Fig. 13.2). The central neck dissection includes the paratracheal nodes both ventral and dorsal to the recurrent laryngeal nerve. These nodes may be a cause of recurrent laryngeal nerve palsy in node-positive thyroid cancer. The upper parathyroid glands often are preserved in situ, whereas this is unfeasible most of the time for the lower parathyroid glands. Submental and submandibular nodes are routinely dissected in MTC but not in PTC.

Lateral Neck Compartment

Starting at the lateral aspect of the jugular vein, the dissection is carried forward toward the venous angle. Divided lymphatic vessels are meticulously ligated, especially on the left side, to prevent lymphatic leakage at the venous angle from injuries to the thoracic or right lymphatic duct, which are a major cause of morbidity. To confirm the continued function of motor nerves running through the lateral compartment (e.g., accessory or phrenic nerve), the same neuromonitoring technique can be used as for the recurrent laryngeal or vagal nerve. In MTC, the dissection routinely includes level II–V. In PTC without evidence of level I and II involvement, the dissection may be restricted to level III–V [173]. The sternocleidomastoid muscles are preserved unless they have been invaded by thyroid cancer.

Mediastinal Compartment

Transsternal LND is warranted only for confirmed mediastinal nodes or extrathyroidal extension of the primary cancer into the infrabrachiocephalic mediastinum. A complete median sternotomy is required for full exposure and complete removal of all fatty tissue with the thymus and mediastinal nodes down to the tracheal bifurcation and the azygous vein. Special attention is paid to

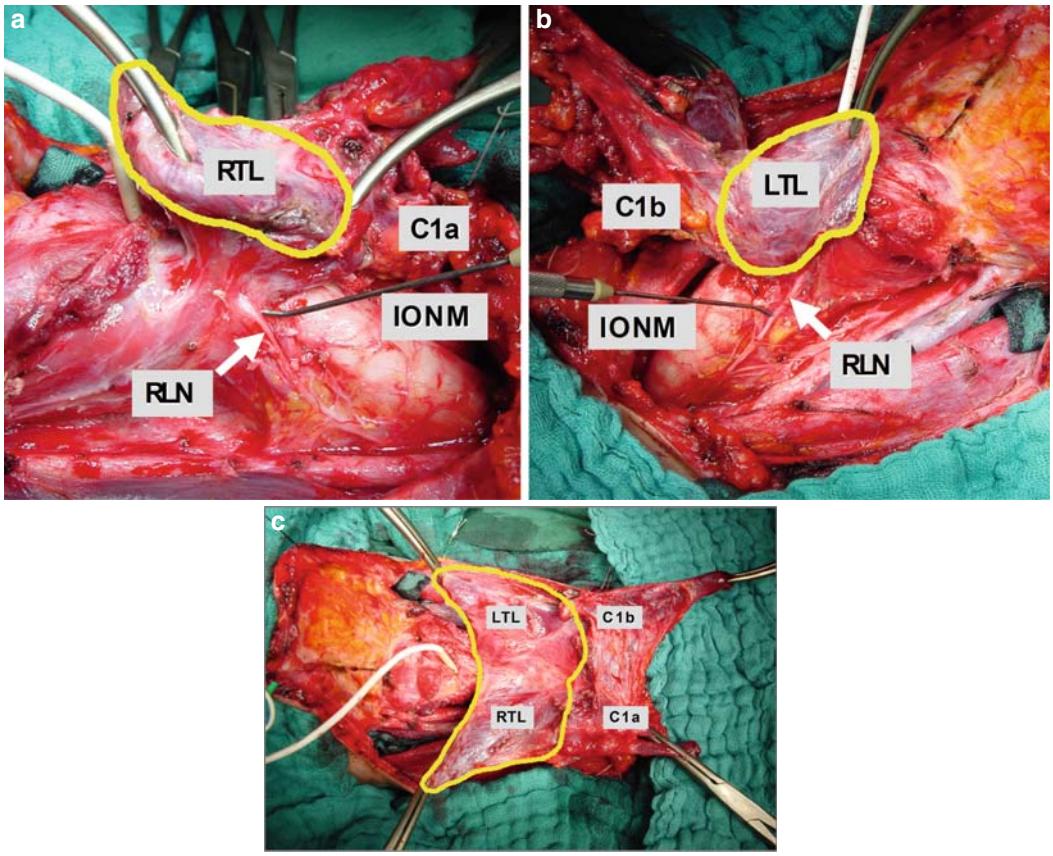

Fig. 13.2. Compartment-oriented microdissection of the central compartment [24] combined with total thyroidectomy. RLN, recurrent laryngeal nerve; IONM, intraoperative neuromonitoring electrode; LTL, left thyroid lobe; RTL, right thyroid lobe; C1a, right central neck compartment; C1b, left central neck compartment.

the course of the recurrent laryngeal nerve on either side, which can be highly variable, and to the mediastinal passage of the phrenic nerve. Either nerve must be carefully preserved. When the central neck compartment and the upper mediastinal compartment are dissected in one session, they are removed together as one contiguous surgical specimen (Fig. 13.3).

Surgical Concept

Inadequate lymph node surgery is the main cause of recurrent thyroid cancer [143]. It more seriously affects those patients who initially present with gross rather than occult disease [24, 41, 60]. Although there are no good data regarding the impact of hospital or surgeon expertise on outcome in thyroid cancer, it is reasonable to assume that professional training and the experience of operating surgeons and their institutions decreases the rates of tumor recurrence and surgical morbidity and perhaps increases survival [174–178].

Typical of rare diseases such as thyroid cancer, retrospective studies may be the sole evidence base to derive treatment recommendations. When more than one treatment option is available, the grade of each recommendation must be considered. Unfortunately, retrospective studies are not well controlled most of the time because there is often just one intervention or, when two or more interventions are

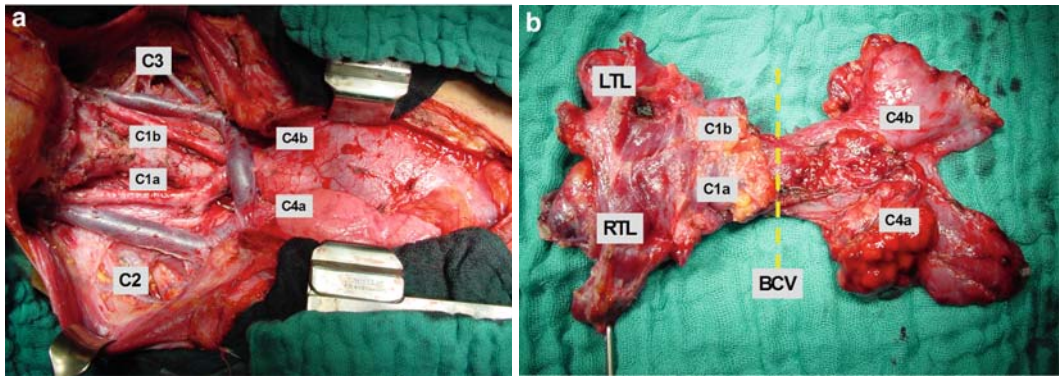

Fig. 13.3. Transsternal four-compartment microdissection with combined microdissection of the central and mediastinal compartment [24]. LTL, left thyroid lobe; RTL, right thyroid lobe; (C1a) right central neck compartment; (C1b) left central neck compartment; (C2) right lateral neck compartment; (C3) left lateral neck compartment; (C4a) right upper mediastinal compartment; (C4b) left upper mediastinal compartment; BCV, virtual level of the left brachiocephalic vein.

compared, assignment to treatment was not randomized. As a consequence, unmeasured and unmeasurable confounding factors cannot be controlled for and may produce spurious results and conclusions. The "best treatment" is selected based on "best available evidence" and the patient's personal values and preferences.

The following concept summarizes current evidence regarding surgical treatment strategies (Table 13.3). This concept draws on current literature, international practice guidelines [6–8], and the authors' experience with some 1500 patients with thyroid cancer seen over a 13-year period at a single institution, many of whom underwent reoperations for recurrence [179].

Papillary Carcinoma

When one weighs the considerable morbidity of LND (hypoparathyroidism, recurrent laryngeal nerve palsy) against the low risk of locoregional recurrence, there is no indication for routine LND for occult ($\leq$10 mm) node-negative PTC unless adverse features are present, such as invasion of the thyroid capsule, multifocal tumor growth, diffuse-sclerosing or tall cell variants, or distant metastases. For all other PTC, compartment-oriented mircodissection (COMD) of affected compartments is recommended. There is some evidence to suggest that routine dissection of both lateral neck compartments may be beneficial in high-risk PTC with special risk factors, such as locally advanced or poorly differentiated tumor growth, multiple central and lateral node metastases ipsilateral to the primary tumor, or the diffuse sclerosing variant.

For completion, all affected compartments should be dissected in patients with multiple node metastases who initially did not undergo compartment-oriented microdissection and now have locoregional recurrence. Single-node recurrences do not necessitate extensive reoperations.

Follicular Carcinoma

In FTC, node metastases are harbingers of systemic disease. Routine LND therefore is not a key element of the surgical strategy. In node-positive FTC with multiple node metastases, a regional- or compartment-oriented approach is favored over a focused approach or excision of single nodes ("berry picking"). The key objective of lymph node surgery for FTC is local control.

Medullary Thyroid Carcinoma

Stage is the single most powerful predictor of outcome in MTC [114]. When stage is adjusted for, there is no difference between sporadic and hereditary MTC. Both forms of MTC are treated equally, especially node-positive tumors. Subtle differences in treatment may exist, for instance

Table 13.3. Surgical concept of lymph node surgery in thyroid cancer

Tumor type	Extent of disease	Surgical strategy
PTC	**at first surgery:**	
	– occult PTC (<10 mm), solitary, N0, M0, T1	no routine LND
	– all other PTC	routine COMD C1 and COMD of affected compartment(s)
	– node-positive PTC with special risk factors (e.g., T1-3b, T4, diffuse sclerosing, tall cell, poor differentiation)	COMD C1–3
	at reoperation:	
	– solitary LNM	focused or regional LND
	– multiple LNM	COMD
FTC	**at first surgery:**	
	– minimally or widely invasive FTC, no LNM	no routine LND regional LND
	– solitary LNM	COMD of affected compartment(s)
	– multiple LNM	
	at reoperation:	focused or regional LND
	– solitary LNM	regional LND or COMD of involved compartment(s)
	– multiple LNM	
MTC	**at first surgery:**	
	gene carriers, bCT ↔, sCT ↔	no LND
	bCT ↔, sCT ↑	COMD C1
	bCT ↑	COMD C1 – 3
	noncarriers,	
	<5 mm, or sCT < 500 pg/ml	COMD C1
	>5 mm, or sCT > 500 pg/ml	COMD C1–3
	solitary or multiple LNM	COMD C1–3
	at reoperation:	
	– solitary LNM	COMD C1–3
	– multiple LNM	COMD C1–3

TNM, classification to TNM supplement, third edition [28];
COMD, compartment-oriented microdissection;
C1, central neck compartment according to the compartment classification [24], comprising levels I and VI of the classification of American Academy of Otolaryngology, Head and Neck Surgery [27];
C1–3, central and both lateral neck compartments according to the compartment classification [24], comprising levels I–VI according to the classification of American Academy of Otolaryngology, Head and Neck Surgery [27];
LND, lymph node dissection;
LNM, lymph node metastases;
bCT, basal calcitonin;
sCT, stimulated (peak) calcitonin;
↔ normal serum levels
↑ elevated serum levels

in the early phase of MTC because occult hereditary MTC, unlike sporadic MTC, arises from neoplastic C-cell hyperplasia. Basal and stimulated calcitonin levels were shown to differ between node-negative and node-positive hereditary (but not in sporadic, occult MTC), more than age or type of the respective germline mutation [180]. The risk of node metastases

is almost nonexistent in gene carriers with normal basal calcitonin levels but increases significantly when these levels are above normal [125–128, 181, 182]. For personalized prophylactic surgery, the gene carrier's age, type of mutation [65, 131], and basal calcitonin levels are helpful when considering the need for additional node dissection during total thyroidectomy. In hereditary and sporadic MTC alike, the risk of node metastases increases with primary tumors >5 cm [183] and stimulated calcitonin values >500 pg/ml [180]. In this setting, routine dissection of the central and both lateral neck compartments is advised.

When MTC patients develop locoregional recurrence in the neck after a less than compartment-oriented microdissection, the central and both lateral neck compartments should be dissected for completion altogether. Conversely, focused or regional approaches are usually adequate for recurrent MTC after previous compartment-oriented microdissection. The prognosis of patients with recurrent MTC obviously hinges more on calcitonin-doubling times [112] and CEA levels [113] than on initial tumor stage. Unless they are high, elevated calcitonin and CEA levels are compatible with excellent long-term survival. In patients with hypercalcitoninemia, new imaging techniques, especially PET and contrast-enhanced CT and MRI, localize previously "occult" disease more precisely than ever before. These advancements in imaging have enabled one to better differentiate between patients with solely local disease, which is amenable to surgery, and systemic disease.

Conclusion

Frequently, extension of the primary tumor through the thyroid capsule and lymph node metastases are early events in thyroid cancer, especially with PTC and MTC. Regardless of the effect on survival, lymph node metastases are a frequent source of locoregional recurrence, which is often caused by an inadequate initial operation. Lymph node metastases in the neck and mediastinum are associated with additional morbidity, from both the tumor and the surgical efforts required to remove it. Early detection and compartment-oriented microdissection hold the keys to cure in thyroid cancer, calling for more professional training in the indications for, and the extent and technique of, compartment-oriented microdissection.

Metastatic thyroid cancers do not follow the path of classic head and neck cancers. As a corollary, a classification of locoregional nodes originally devised for head and neck cancer cannot simply be translated to thyroid cancer by analogy. Tailored to the locoregional lymph node system of the thyroid, the compartment classification is more suitable for thyroid cancer surgery and is the only system which includes the infrabrachiocephalic upper mediastinal nodes.

Involvement of the lateral compartment of the ipsilateral neck is almost as common as central neck involvement, not just in PTC but also in MTC. From an oncological point of view, dissection of the central neck compartment alone is more diagnostic than therapeutic. Central LND may be adequate for early thyroid cancer with a few positive nodes. For previously untreated tumors with multiple node metastases, the central neck compartment and the lateral neck compartment ipsilateral to the primary tumor are dissected as a minimum. Although routine dissection of both lateral neck compartments for node-positive MTC is widely accepted, its use is more controversial in PTC unless these compartments are clinically affected.

With the introduction of the revolutionary concept of DNA-based prophylactic thyroidectomy [184, 185], it has become apparent that node metastases in hereditary MTC cannot be reliably predicted by the gene carrier's age or type of mutation. To minimize both overtreatment and undertreatment of carriers, basal calcitonin levels should be determined. Normal basal levels suggest the adequacy of total thyroidectomy alone, unless there is clinical evidence to the contrary, whereas elevated basal levels indicate a need for additional LND.

For palliation of thyroid cancer, the role of lymph node surgery within a multidisciplinary effort is limited. In locally advanced thyroid cancer, LND can be effective in reaching local control in the neck, silencing the "pacemaker of the disease."

In conclusion, surgeons are the champions of local control of thyroid cancer. Commanding an armamentarium of highly sensitive and effective tools, they tailor the extent of surgery to the extent of disease. Through the timely delivery of adequate initial operations, surgeons can reduce the number of reoperations for recurrent thyroid cancer, preventing unnecessary morbidity from local tumor invasion and corrective surgical procedures.

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14

Management of the Laryngeal Nerves and Voice

David J. Lesnik and Gregory W. Randolph

Introduction

One's voice is a fundamental identifying human trait. Changes in voice raise great concern with most patients considering thyroid surgery, even if they are not professional singers or vocalists. Any discussion of voice in surgery must begin with a review of laryngeal anatomy, neurolaryngology, and mechanism of normal voice production. The thyroid surgeon must take great care in preserving function in all cases. However, even the expert surgeon will encounter laryngeal nerve injuries and voice deficits. Knowledge of the various diagnostic tests and management techniques is essential to comprehensive surgical care.

Anatomy of the Larynx and Laryngeal Nerves

The larynx includes the cartilaginous and ligamentous skeleton, the intrinsic and extrinsic musculature, neurovascular supply as well as the mucosal lining of the endolarynx. One may consider the hyoid bone, the epiglottis, the thyroid, and cricoid cartilages (including their ligamentous and membranous attachments) as the framework of the larynx. The larynx has three primary functions: respiration, airway protection, and voice production.

The majority of laryngeal musculature is involved in vocal cord adduction (movement of the vocal cord to the midline, toward closing the glottis) to protect the airway from aspiration, but also to regulate respiration and speech. The intrinsic muscles of the larynx include the muscles of the true vocal folds (vocalis and the thyroarytenoid muscles) and the muscles attaching the arytenoid, cricoid, and thyroid cartilages (the lateral and posterior cricoarytenoid muscles, the interarytenoid muscles, and cricothyroid muscles). The posterior cricoarytenoid muscles are the main abductors (movement of the vocal cord away from the midline, toward opening the glottis) of the true vocal fold resulting in lateralization of the cords for respiration.

The inferior or recurrent laryngeal nerve (RLN) emerges from the 10th cranial nerve at different points on the left and right sides. On the left, it leaves the vagus nerve in the thoracic cavity and, traveling anterior to posterior, crosses under the aortic arch and extends cranially in a relatively medial aspect of the left tracheoesophageal groove deep to the thyroid gland. The right vagus passes anterior to the subclavian artery in the right neck bases. The right RLN derives from the vagus just below the subclavian artery crossing and extends cranially from deep to the subclavian artery into the right paratracheal region approaching the larynx from a more lateral direction before arriving at the right laryngeal entry point. Bilaterally, the RLN leaves the thyroid surgical field at the point termed the laryngeal entry point, diving deep to the lowest most fibers of the

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inferior constrictor muscle at the lateral aspect of the cricoid cartilage's lower edge. Within the larynx, the RLN travels behind the cricothyroid joint deep to the inferior constrictor muscle. The RLN is a mixed nerve containing an average of 1200 myelinated axons and thousands of unmyelinated axons. It provides both sensory and motor innervation to the larynx. The sensory division provides sensation to the internal larynx inferior to the glottis (Fig. 14.1) [1].

Superior laryngeal innervation in the form of the left and right superior laryngeal nerves (SLNs) arises from the vagus in the neck and is also of great importance to the thyroid surgeon. The SLN leaves the vagus nerve at the nodose ganglion and travels along the medial side of the carotid artery and enters the larynx at the thyrohyoid membrane, just above the upper margin of the thyroid cartilage. This internal branch (IBSLN) relays afferent sensory information from the supraglottic larynx. Its function is important in the sensory component of swallowing and in the prevention of aspiration via the glottic closure reflex. The external branch (EBSLN) is the sole motor component of the SLN and provides innervation to the paired cricothyroid muscles which change the relative positions of the thyroid and cricoid cartilages resulting in tensing of the true vocal folds and elevation in vocal pitch.

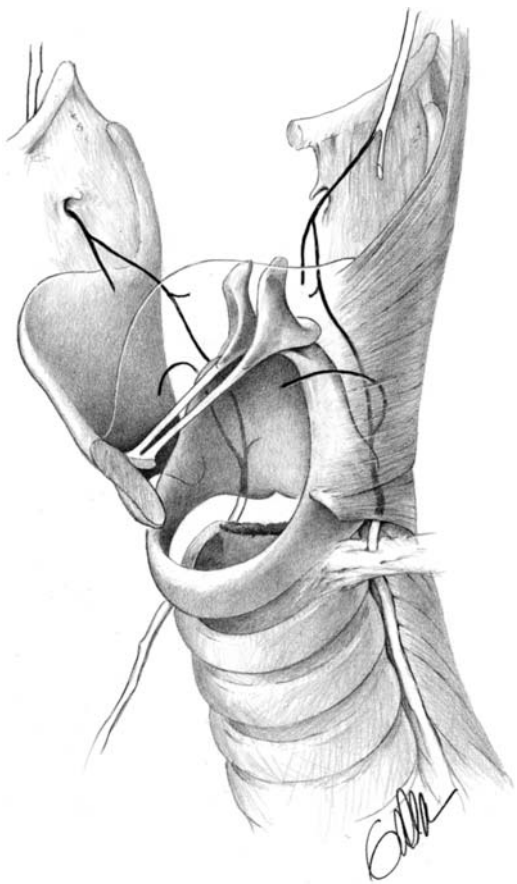

Fig. 14.1. Artistic rendition of the laryngeal skeleton demonstrating cartilaginous and ligamentous framework with course of laryngeal nerves. Reprinted from Randolph, G.W., ed. Surgery of the thyroid and parathyroid glands. Philadelphia: Saunders, 2003. This figure was published in Surgery of the thyroid and parathyroid glands, Randolph GW, ed. Copyright Elsevier 2003. Reprinted with permission.

The motor supply to the extrinsic laryngeal strap muscles (including the sternohyoid, sternothyroid, and omohyoid muscles) originates in the submental triangle from the hypoglossal nerve and travels inferiorly as the ansa hypoglossi in association with the carotid sheath. The fibers of the ansa are found most readily on the ventral surface of the jugular vein at the lateral margin of the strap muscles.

Vascular supply to the larynx arises from the external carotid system via the superior thyroid artery and then as the superior laryngeal artery that enters the larynx along with the IBSLN at the thyrohyoid membrane. The inferior laryngeal artery is a branch of the inferior thyroid artery off the thyrocervical trunk. Veinous drainage extends into the jugular venous system and brachiocephalic vein via the superior and middle thyroid veins as well as inferior thyroid veins, respectively.

The lymphatic drainage of the larynx and perithyroidal region follows the venous drainage system. The supraglottic drainage (i.e., above the vocal cords) is primarily bilateral draining along the jugular chain (Levels II, III, and IV, i.e., upper, mid-, and lower jugular regions). Glottic lymphatic drainage is primarily unilateral to the mid- and lower jugular chain (Levels III and IV). The subglottic drainage (i.e., below the vocal cords) is also bilateral to the central neck, low jugular chain, and posterior triangle (Levels IV, V, and VI)

Voice Production

Phonation occurs after the efferent signals generated in the motor cortex proceed via bilateral brainstem nuclei (nucleus ambiguous) through

left and right branches of the vagus nerve (CN X) to reach the larynx. Signals terminate in the motor end plates of the intrinsic laryngeal muscles via the left and right RLNs, resulting in laryngeal muscular contractions. The entire efferent process inherent in voice production can be accomplished within 90 ms, and requires close coordination with respiratory musculature via central nervous system motor neurons [1].

Lalwani describes voice as a product of the semicyclical vibrations of the vocal cords [1]. Normal voice emanates from oscillations of the vocal cord mucosa, as it moves relative to the underlying cordal musculature. This cordal vibration is basically controlled by vocal cord muscular tension, elastic vocal cord properties, and aerodynamic forces of subglottic air as it passes through the relative constriction of the partially closed glottis during phonation; cordal vibration is generated as the air expelled under pressure from the lungs passes between the vocal cords and sets the cords into an oscillatory motion [1]. Voice's volitional component derives from modification of the muscular dynamic of the cord and surrounding larynx through varying RLN and SLN neural tone. Vibration of the vocal cord is age and gender dependent. Pathologic voice quality can result when any of these components are affected (i.e., muscles, neural supply, mucosa, the submucosal space, vascular elements, or surrounding cartilage framework).

In addition to the actions of the intrinsic laryngeal musculature, the entire larynx is subject to vertical motions produced by the action of the paired extrinsic laryngeal musculature (strap muscles). These vertical laryngeal motions are important in phonation, singing, respiration, yawning, and especially crucial in swallowing. According to Lalwani, when this vertical laryngeal movement is affected, voice production may be severely compromised even if the glottis looks "normal" on a routine ear, nose, and throat exam [1]. Others have suggested that handling or even resection of the straps create no measurable problems with voice. We feel strap muscle changes after thyroid surgery can have significant transient effect on voice but little long-term significant effects for most nonprofessional voice users.

Importance of Preoperative Laryngoscopy

Preoperative laryngoscopy is certainly a valuable mode of assessment the thyroid surgeon can employ with relative ease. A complete view of the patient's laryngeal function may elucidate the full extent of disease and facilitate fully informed surgical decision making and success. Direct laryngoscopy with assessment of movement of the vocal fold and arytenoids is difficult without use of a general anesthetic. However, indirect fiberoptic laryngoscopy is a simple and well-tolerated office procedure of great utility in both revision and first-time surgical cases. One may use a pediatric or adult fiberoptic laryngoscope (2–4 mm diameter) passed transnasally after topical decongestion to attain an expeditious evaluation of laryngeal anatomy and function.

The appearance of the larynx should be symmetrical at rest and in phonation. Unilateral vocal cord paralysis is typically marked by a thick, short, immobile true vocal fold with associated anterior prolapse of the arytenoid. Careful observation will often reveal inferior displacement of the injured cord out of the normal plane of mucosal apposition relative to the normal cord. Breathiness and vocal fatigue will often result as the vocal folds will not meet in the midline upon volitional adduction. The rare bilateral vocal lesion results in bilaterally medially positioned, immobile vocal cords with little to no abduction. These patients often present with serviceable voice but with signs of upper airway distress due to a severely narrowed glottic aperture. Unilateral EBSLN injuries which limit vocal range and pitch may be observed as a rotation of the posterior larynx towards the side of the injury [2]. The affected cord is said to be bowed and somewhat lower as well.

Randolph and Kamani studied a series of 365 patients prior to undergoing thyroid surgery including a subset of 21 patients found to have malignant invasion of the RLN intraoperatively. Preoperative vocal cord paralysis was found in 70% of patients with invasive disease versus 0.3% of patients with benign thyroid lesions. Only a minority (33%) of patients with invasive disease presented with voice changes and only 25% with evidence of

vocal cord paralysis on CT [3]. These findings underscore the need for preoperative laryngoscopy in all patients undergoing thyroid surgery as imaging techniques and clinical presentation are often insufficient in providing a complete estimation of laryngeal deficits. The basic issue is that preoperative vocal cord paralysis may be completely asymptomatic. The knowledge of preoperative paralysis is extremely helpful in surgical planning of malignant thyroid lesions, and is critical for complete informed consent. For example, if a preoperative vocal palsy is present and contralateral surgery is planned, then the specter of a possible tracheostomy must be raised with the patient whereas this may not otherwise be a common consideration.

Farrag examined 340 patients undergoing thyroidectomy preoperatively to determine the incidence of vocal cord impairment prior to surgery. Twenty-two of 340 patients were found to have cord impairment and over 30% of these patients were completely asymptomatic. Using patient-reported voice symptoms as a screening test to predict vocal fold motion impairment in this patient population, results revealed that this clinical screening test yielded a sensitivity of 68%, specificity of 91%, positive predictive value (PPV) of 31%, and negative predictive value (NPV) of 98%. It is also remarkable that, in this study, 5/22 or 22.5% of patients had vocal cord impairment contralateral to the side of the thyroid lesion [4]. These findings clearly demonstrate that patient history alone is insufficient in understanding laryngeal impairment nor will it fully apprise the surgeon or patient of the potential surgical risks of any subsequent procedure. Preoperative laryngoscopy will contribute much to these considerations and is necessary in all cases.

Nerve Monitoring in Thyroid and Parathyroid Surgery

Initial EMG endotracheal tube experimentation employed designs using a foil-wrapped endotracheal tube [5, 6]. Many electrode designs and monitoring systems have been used over the years but we prefer the endotracheal tube surface electrodes format and a monitoring system with visual EMG waveform information. When the tube is in the normal position and the cuff is in the subglottis, the surface electrodes are in contact with the medial aspect of the bilateral true vocal folds. Grounding electrodes are placed on the patient's shoulders and are interfaced, together with the recording electrodes, to the monitor via a connector box (Fig. 14.2). After tube placement, impedance values may be checked on the monitor. Values of less than 5 kΩ

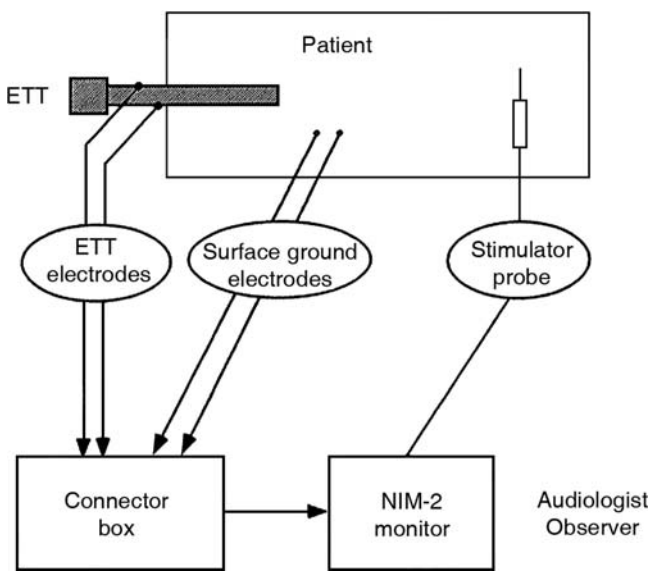

Fig. 14.2. Schematic diagram demonstrating arrangement of the NIM-2 recurrent laryngeal nerve monitoring system. This figure was published in Surgery of the thyroid and parathyroid glands, Randolph GW, ed. Copyright Elsevier 2003. Reprinted with permission.

with an imbalance of less than 1 kΩ reflects good electrode-mucosa contact and is generally recommended [7]. A sterile, hand-held stimulator probe is connected to the monitor as well and is used to deliver the adjustable stimulus (0.5–2 mA) to the RLN. It delivers four stimulation bursts per second with stimulation duration of 100 μs. This system allows passive and evoked monitoring of the thyroarytenoid muscles via both visual and audio feedback from the EMG monitor to the surgeon during thyroid or parathyroid surgery (Fig. 14.3) (Medtronic NIM-2, Jacksonville, FL). We have developed an algorithm to assist in monitoring system setup (Table 14.1).

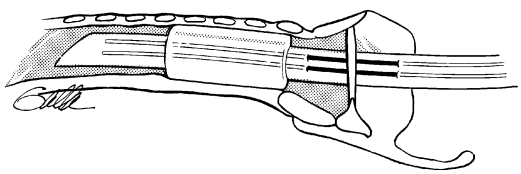

Fig. 14.3. The endotracheal tube is positioned so that the dual electrode is facing the surface of the true vocal fold. This figure was published in Surgery of the thyroid and parathyroid glands, Randolph GW, ed. Copyright Elsevier 2003. Reprinted with permission.

Troubleshooting

If EMG response is lost during stimulation, the surgeon should first check for laryngeal twitch. Laryngeal twitch is accessed through palpation of the posterior aspect of the cricoid cartilage during stimulation of the RLN. The examining finger sensed the posterior cricoarytenoid muscle's contraction. If the twitch can be palpated, then equipment failure should be suspected. Grounding electrodes must be checked, tube position confirmed, and probe function checked by replacing the stimulator. If the twitch is not detectable, then the monitor must be checked for current return, neuromuscular blockade must be ruled out, and, of course, neural injury must be considered [8].

False-positive EMG responses may occur if an excessive level of stimulating current is used resulting in shunting of current to the RLN typically along small vascular structures that form bridges to the nerve. However, the amplitude is often lower than direct neural stimulation in these cases. Reducing the stimulus can rectify this problem. Some believe that bipolar neural stimulation may also reduce false-positive responses [9].

Table 14.1. Practical tips for monitoring system setup [8]

1. Succinylcholine or other short acting paralytic agent allows full relaxation for good ET tube position with quick return of EMG activity
2. Care must be taken to position the surface electrodes at the level of the glottis and the ET tube cuff in the subglottis. Colored markers on the tube can help with this
3. Position patient with extension as necessary prior to securing ET tube
4. The grounding electrodes for each of the two recording endotracheal tube electrodes as well for the stimulus probe are secured to the patients shoulder with adhesive
5. Check for:
   a. Respiratory variation in baseline EMG tracing. Respiratory variation consists of small waveforms between 30 and 70 μV (variation in baseline) seen on bilateral electrodes and confirms good tube position. This occurs after paralytic induction agent has worn off and before deep inhalation anesthesia has been achieved
   b. Impedance of less than 5 kΩ with impedance imbalance of less than 1 kΩ.
   c. If conditions of a and b are not met, then visual confirmation of tube position should be achieved
   d. Tube should be secured with tape at the lip after respiratory variation is evident in the positioned patient. Support to prevent tube migration, typically inward, should be provided
6. Monitor settings:
   a. Event threshold (EMG response), 100 μV
   b. Stimulator probe, 1 mA
7. Surgical field notes:
   a. Test stimulator on strap muscle to confirm twitch and that current is received on monitor
   b. Visually identify vagus nerve and confirm true positive before accepting any stimulation as negative
   c. No structure in the lateral thyroid region should be clamped, ligated, or cut until the RLN is identified both visually and electrically

Spontaneous activity may be related to specific surgical maneuvers and should prompt careful consideration of technique. Stretching or clamping of the nerve, in addition to the effects of cautery adjacent to the nerve, may result in trains of spontaneous EMG response that should resolve with cessation of the responsible maneuver [8]. Multiple studies, including those of the senior author, have demonstrated the safety of repetitive stimulations using constant current, pulsed stimulation in the 1–2 mA range [10–13].

Advantages of Nerve Monitoring

Some studies have determined that routine identification of the RLN is associated with lower rates of injury [8]. Monitoring may reduce the incidence of intraoperative nerve injury, and yet, it is not used universally [14]. Nerve monitoring is a logical extension of anatomic nerve visualization. We feel RLN monitoring represents a very useful technical development that may greatly aid the surgeon in identifying and protecting the RLN during surgery in this area, especially in difficult cases, e.g., large goiter, inflammatory disease, extensive malignancy, or reoperative cases. RLN monitoring adds a new functional dynamic to thyroid surgery and adds to visual information RLN monitoring can be considered in has three modes: (1) to facilitate neural identification, (2) to aid in neural dissection, and (3) to prognosticate regarding postoperative neural function.

Improved RLN Identification and Dissection

First, for initial nerve localization before definitive identification, the blunt-tipped stimulus probe may be used at higher intensity (e.g., 2 mA) to probe and "neutrally map" the soft tissue of the RLN triangle starting at a more superficial level proceeding more deeply. This technique often expedites identification of the proximal portion of the RLN through targeted dissection. In addition, once the RLN is identified, dissection of the nerve can be facilitated especially through difficult surgical fields (such as in a reoperative or radiated field or along Berry's ligament in cases of thyroiditis) through intermittent test stimulation before division of soft tissue structures adjacent to the RLN. Song points out that monitoring can detect neural discharge during retraction and may help prevent neuropraxic traction injury [15]. Monitoring can also signal return of function after a traction injury. Thomusch et al. prospectively studied over 4000 patients undergoing thyroidectomy with and without nerve monitoring. In their study, patients who underwent surgery with intraoperative RLN monitoring had lower rates of both temporary and permanent RLN injury (1.4 and 0.4%) compared with patients having surgery without monitoring (2.1 and 0.8%) [16].

Prognostic Function

It is well known that the surgeon's eye is not reliable in predicting injury to the RLN in thyroid surgery [17–19]. This leads to an underestimation of RLN injuries. Caldarelli has found that injury to the RLN may be caused by stretch/traction, pressure, crush, electrical injury, ischemia, and suction injury in addition to transection [8]. The bulk of nontransection injuries are hard to predict intraoperatively by visual assessment alone. If ispsilateral RLN injury goes unrecongnized, the patient is at increased risk if bilateral dissection is planned. Empiric recommendations have been made to perform prophylactic tracheotomy in "high-risk patients" and in "extensive resections" [20, 21]. Nerve monitoring can help provide information to stage complex surgery and avoid bilateral RLN injury and possible tracheotomy .

The study of intraoperative neural prognosticating for the RLN is based in part on substantial experience with neural monitoring for predicting injury to the facial nerve in cerebellopontine angle surgery. These studies have suggested that elevation in stimulation threshold after surgical manipulation was related to postoperative deficit. In analyzing data from over 1400 human cases as well as those from a canine model of RLN injury, the senior author has observed that in nontransection injuries to the RLN that result in postoperative vocal fold immobility, a decrease in amplitude of the evoked response is seen with less significant changes in latency and stimulation threshold [8]. This would suggest that some fibers are intact to conduct the signal, but that a significant number have been injured resulting is lower

amplitude. However, studies by Eisele have suggested that changes in stimulation threshold after thyroidectomy correlate with postoperative deficits in function. Increases in threshold by as little as 0.1 mA have led to postoperative deficit. The greater the threshold shift, the longer the deficit can be expected. [22] Thomusch et al. also analyzed the reliability of monitoring for predicting RLN dysfunction in 15,403 nerves at risk. They found that an intact stimulation signal was 99.6% accurate in predicting normal postoperative nerve function. This can provide useful information and reassurance for the patient and the surgeon. [23]

The senior author has developed criteria that, when present, accurately predict normal neural function postoperatively. Study of intraoperative EMG data from125 patients with normal postoperative RLN function has provided EMG criteria that will predict normal postoperative laryngeal function when present. These are (1) initial setup criteria which confirm that the nerve has been identified and that the monitoring system is functioning properly and (2) final EMG readings that predict normal postoperative function [8]. If these are met, it should result in complete avoidance of the complication of bilateral vocal cord paralysis, even in cases of transient injuries. If the first criterion is not met, then the surgeon must check the system connections or consider the possibility that he has not found the nerve. If the initial criteria are met but the final EMG criteria are not, then a neural injury is possible. The surgeon should first check for laryngeal twitch. If present, then neural injury has not occurred and the tube is likely malpositioned. If the twitch is not present, then one should consider the following: (1) problem with current delivery, (2) displacement of ground electrodes, (3) connection problem at connector box, (4) stimulator probe malfunction, (5) neuromuscular blockade, (6) and finally neural injury [8]. Any correctable problems should be sought, e.g., suture impingement on the nerve. However, postoperative paralysis should be expected and the surgeon must consider postponement of the contralateral procedure. There are cases which are associated with higher rates for RLN paralysis for which monitoring is especially helpful (Table 14.2). It is of note, however, that not all difficult cases can be identified preoperatively. Familiarity with the equipment is also improved through routine application.

Monitoring the External Branch

Rates of injury to the EBSLN are between 9 and 14% [8]. Some authors recommend the use of EBSLN monitoring via cricothyroid muscle needle electrode in "high-risk" cases. We feel that the thin cricothyroid muscle would be easily disrupted by needle placement. We favor EBSLN stimulation with visible detection of cricothyroid muscle twitch. It is of note that EBSLN stimulation will give a discrete tracing on the EMG endotracheal monitor (amplitude half that of ipsilateral RLN stimulation with very short latency) due to the EBSLN's extension, the human communicating nerve [8].

In summary, nerve monitoring may assist the surgeon with more rapid and confident identification of the RLN and EBSLN during thyroid and parathyroid surgery. It will also facilitate dissection along the RLN which is

Table 14.2. Cases that may benefit from recurrent laryngeal nerve (RLN) monitoring[8]

1. Cases known to be associated with increased difficult dissection and risk of RLN paralysis:
a. Thyroid cancer
b. Significant lymph node resection
c. Graves' disease/thyroiditis
d. Large cervical or substernal goiters
e. Revision surgery
f. Surgery after external-beam radiation therapy
2. Surgery on an only functioning nerve
3. Strong consideration for *all* cases:
a. Many difficult cases cannot be predicted based on preoperative data (e.g., nonrecurrent RLN)
b. Any bilateral case. Prognostic testing on first side allows safe, contralateral surgery without bilateral vocal cord paralysis

especially useful in certain cases such as a distally branching RLN or in cases of adhesive ligamentous attachments (Berry's ligament). As discussed, it may be used to prognosticate postoperative function and impact the decision to perform bilateral surgery. When using endotracheally based systems, attention to detail and confirmation of tube position preoperatively is essential. It must always be remembered that the monitor is not a substitute for careful surgical technique and meticulous hemostasis.

Surgical Maneuvers to Avoid Injury to EBSLN

This delicate neural structure travels just lateral to the thyroid cartilage on or just under the lateral surface of the inferior constrictor muscle in the cricothyroid space. Aggressive retraction or cautery near the superior pole in the cricothyroid space may lead to injury. The cricothyroid muscle can also be injured directly through aggressive dissection or cautery on the anterolateral cricoid region. The EBSLN may be entrapped during dissection of the superior pole. En-masse division of the superior pedicle may lead to transection. We favor individual dissection and division of superior vessels from medial to lateral direction with careful inspection and electric stimulation with cricothyroid muscle observation. Injury results in lack of vocal range and possible changes in pitch as noted above. Exceptional care must be taken to avoid these mistakes.

The EBSLN has significant anatomic variation, and for this reason, some have suggested that the nerve must be visualized in order to prevent surgical injury [2, 24]. We agree that routine identification as a simple and expeditious maneuver that may decrease the incidence of injury significantly [24].

Intraoperative Injury to the SLN

By far the best means of dealing with intraoperative SLN injury is by identification and avoidance as currently, to our knowledge, there have been no reports of neurorrhaphy or reinnervation. Early speech rehabilitation is to be employed in symptomatic patients [25]. This is perhaps the only mode of therapy.

Surgical Maneuvers to Avoid Injury to RLN

Neural injuries to the RLN may be partial or complete and may be temporary or permanent. The RLN may be injured by multiple mechanisms which in turn relate to either patient disease or to iatrogenic injury. Benign processes such as thyroiditis (Graves', Hashimoto's, and Riedel's viral thyroiditis), the solitary nodule, multinodular goiter, parathyroid adenoma, and substernal goiter may surround and or infiltrate the nerve with or without paralysis. The incidence of vocal fold paralysis in patients with benign thyroid disease is approximately 1% or less [26, 27]. Studies have also shown that 38–89% of these cases of paralysis will recover following surgery and that recovery is more likely in cases of paralysis of shorter duration [26]. It is worth noting that in these cases of gradual growth, there is often no symptomatology as the opposite vocal fold may compensate slowly to obscure any clinical manifestations.

There have been many studies of involvement of the RLN by malignant tumors. The overall incidence of local invasion with papillary cancer is 16% with the RLN being the second most common site of invasion after strap muscle invasion [28, 29]. Falk and McCaffrey studied 262 patients with invasive well-differentiated thyroid carcinoma. Of these, 123 had invasion of the RLN. They found no difference in survival between patients who had their nerve resected versus those who did not if postoperative radioiodine and suppressive T4 was employed. Most patients failed distantly if they failed at all [30].

Most evidence suggests that a nerve that is preoperatively paralyzed and infiltrated with carcinoma will not recover function if preserved at surgery. Given this fact, we feel it should be sacrificed for oncologic benefit. RLN paralysis from thyroid lymphoma may be an exception to this generalization as nerve function may return following nonsurgical treatment of lymphoma [30].

If the nerve is functional preoperatively but found to be infiltrated at surgery, then every attempt should be made to maintain its anatomic integrity unless it would lead to leaving gross malignancy behind. It should be kept in mind that radioiodine therapy and T4 suppression represent possible modalities for

treatment of residual microscopic disease. It is clearly imperative for the surgeon to be aware of the preoperative status of the vocal fold before undertaking any surgery. This evaluation is accomplished by preoperative indirect laryngoscopy.

Routine Identification

As stated above, modern studies have agreed that routine identification of the RLN during thyroid surgery will result in a lower incidence of nerve injury and associated voice changes. Therefore, it is advisable to definitively identify the nerve in every case. Various approaches exist to do this.

Most commonly, the nerve is identified in the recurrent triangle after limited lateral dissection of the thyroid lobe. It is located between the common carotid artery and the trachea, at a level inferior and ventral to the inferior thyroid artery. The nerve monitor may assist with this as previously discussed through the above described neural mapping technique. It can then be dissected superiorly to its laryngeal entry point, so that the ligamentous attachments of the thyroid lobe are divided with the nerve in view. We favor this lateral approach for routine first time surgery.

It may also be identified more inferiorly before significant thyroid lobe dissection. This approach is helpful with large goiters revision cases and where a lateral approach is more difficult. Once found, the RLN is then dissected superiorly to the laryngeal entry point. We especially favor this approach in revision cases where scarring may prohibit the routine lateral approach described above. Through this inferior approach, the revision surgeon may find the nerve below the first surgeon's scar.

In cases of goiter, whether cervical or with significant retrosternal component, it may be difficult if not impossible to identify the nerve through the above described lateral or inferior approaches. In these instances, it will be wise for the surgeon to search for the nerve and begin efforts to identify it at the superior pole through the superior approach to the RLN. The superior pole is carefully isolated with attention to the EBSLN. Subsequently, the RLN may be identified superiorly near the laryngeal entry point. The inferior cornu of the thyroid cartilage as well as the lateral edge of the cricoid cartilage are the landmarks of interest. Once identified here, it may be traced proximally as the goiter is dissected and removed (Fig. 14.4).

Nerve Injury

The pathophysiology of RLN injury, like other peripheral neuropathy, may be considered to range from neuropraxia (i.e., mild traction or dissection injury) to full neurotmesis with complete fascicle-perineural disruption and subsequent Wallerian degeneration (i.e., transection injury) as described by Sunderland [31].

Iatrogenic injury may have numerous causes and consequences. Rates of iatrogenic injury may vary widely (1–25%) and are not always easy to interpret for a variety of reasons. RLN injury may be underreported due to failure to recognize injury on the part of the surgeon as well as failure to perform routine postoperative laryngeal exam.

It is important to understand that there are many causes of postoperative voice change without RLN or SLN injury. These non-neural sources of postoperative voice change are almost always temporary but often indistinguishable from neural injury by voice quality alone. Laryngeal exam is essential in distinguishing amongst the various causes of post-thyroidectomy voice change. We have proposed the following system for organizing the causes of postoperative voice change (Table 14.3).

Usually, postoperative dysphonia from non-neural causes is temporary. Most cases of long-term dysphonia, however, will be due to iatrogenic nerve injury. The only way to arrive at accurate estimates of overall true rate of RLN injury is to assess all patients undergoing thyroidectomy both before and after all surgery by indirect laryngeal exam by one versed in laryngoscopy.

For these and other reasons, the true rate of RLN injury must be discussed as temporary and permanent injuries (those lasting more than 6–12 months). The rates of 1% that are quoted in the literature may be biased by underreporting due to lack of laryngeal exam postoperatively. Also rates may vary with pathology and with the particular procedure performed. Injury to the RLN is more common in the following situations: lack of identification at surgery, bilateral surgery, surgery for cancer, surgery

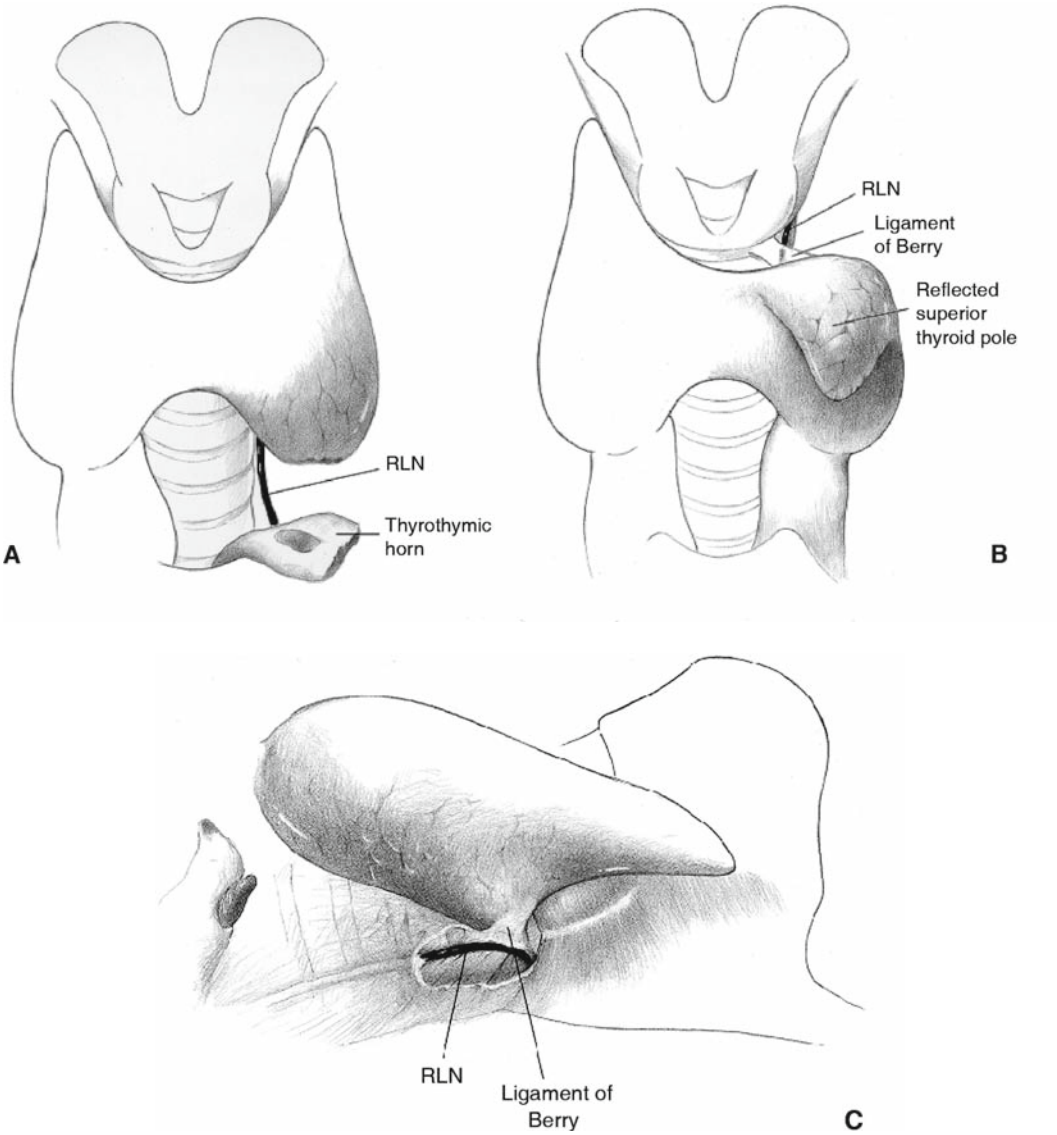

Fig. 14.4. Relationship of the recurrent laryngeal nerve and the thyroid gland. Techniques for nerve identification. (**A**) RLN is identified inferiorly in the recurrent triangle. The inferior pole is reflected superiorly and inferior parathyroid gland is depicted in situ in the thyrothymic horn. (**B**) RLN is identified superiorly near its laryngeal entry point. This technique can be helpful in revision cases and with substernal goiter. (**C**) Lateral view of left thyroid lobe reflected medially. The RLN is seen in the tracheoesophageal groove in close relation with Berry's ligament. This figure was published in Surgery of the thyroid and parathyroid glands, Randolph GW, ed. Copyright Elsevier 2003. Reprinted with permission.

associated with extensive lymph node dissection, surgery for Graves' disease or thyroiditis, revision surgery, surgery associated with substernal goiter, surgery with longer operating times or greater blood loss, and patients brought back for bleeding [8].

The effects of injury on the RLN on the patient are not easy to predict. Temporary lesions will likely result in complete recovery with time. Permanent paralysis may present with mild to severe dysphonia. However, some patients have near normal speaking

Table 14.3. The causes of postoperative voice change after thyroid surgery

1. RLN paralysis or paresis
2. SLN paralysis or paresis
3. Endotracheal associated:
a. Direct vocal cord injury or edema
b. Arytenoid dislocation
c. Paralysis
4. Regional non-neural effects:
a. Strap muscle injury or denervation
b. Global perilaryngeal neural plexus (nonmotor) disruption
c. Global regional scar /fixation
d. Inflammatory change cricothyroid muscle
5. Coincident voice change unrelated to surgery, ex viral neuritis

voices even with complete unilateral paralysis (a reason for underreporting in some studies) while others have significant vocal fatigue and air escape leading to a breathy voice quality, vocal fatigue, and poor projection. Other symptoms include varying levels of dyspnea and possible aspiration. Some patients will present with coughing paroxysm due to chronic aspiration of saliva and others with frank aspiration pneumonia.

Traction Injury

Traction injury is a neuropraxic injury that will often improve with time if the traction is relieved. The nerve monitor allows the surgeon to recognize this type of injury and to make appropriate modifications in technique to improve it. Spontaneous EMG activity is followed by a period of no response to stimulation proximal to the injured site [8].

Crush Injury

Studies in dogs and observations in humans have suggested that nontransection crush injuries need not be repaired and have a reasonable prospect for recovery. In dogs, function may recover in 4–8 weeks [8].

Suture Impingement

It is possible to entrap the RLN with a suture ligation of vascular structures. Once again, this type of injury may easily go unrecognized, but may be revealed through nerve monitoring as it will result in a decrease or cessation of electrical response. The exact point of the injury can be identified through "injury site mapping" of the injured nerve. Stimulation of the RLN at a point proximal to the suture will not result in response whereas stimulation distal to the site of injury will yield a normal EMG tracing [8]. This area can then be examined carefully and the suture removed to provide the best chance for return of normal function. Suture ligation would not be expected to recover if not released.

Cautery Injury

The potential deleterious effects of thermal and electrical energy on peripheral nerves is well known. Monopolar cautery causes significant injury to myelinated and unmyelinated peripheral nerves including marked damage to Schwann cells [32]. We favor limited bipolar cautery with a small fine-tipped bipolar instrument in the area of the ligament of berry, allowing time for the region treated to cool between applications

Intraoperative Resection/ Transection

Before resecting a RLN, it should be remembered that radioiodine and T4 suppression is a viable option in cases of residual microscopic disease, and external beam radiation may play a role in selected patients. In some cases of invasive malignancy, it will be necessary to resect a segment of the RLN. The typical scenario for RLN resection would be an immobile cord on preoperative laryngoscopy and frank gross invasion by malignancy found intraoperatively.

Options for repair would include primary anastomosis or reinnervation procedure. Primary anastomosis employs interrupted 10-0 nylon in the epineurium. Early studies of results after neurorrhaphy by Horsely in 1909 and Leahy in 1929 reported normal postoperative function [8]. More recent studies have recorded return of EMG activity but poor functional results [33,

34]. It appears that adductor function predominates after neurorrhaphy and that paradoxical vocal fold motion can be seen due to misdirection of abductor and adductor fibers [35, 36]. These results may be expected given that adducting fibers outnumber abductors in the RLN and the majority of laryngeal musculature serves an adducting function [37, 38]. On the other hand, some authors believe outcome is better with neurorrhaphy due to improved resting tone of the vocal fold and improved position of the arytenoid cartilage [39].

In cases where primary anastomosis is not possible, reinnervation may be preferable for maintenance of thyroarytenoid muscular tone and improved arytenoid position. Options include reinnervation with ansa cervicalis, phrenic nerve, and vagal nerve. The best option is ansa cervicalis (sternothyroid branch) – RLN anastomosis according to Crumley [40]. This type of repair is ideal after segmental defect from RLN resection in cases of malignant infiltration. This may be performed to the distal main or adductor branch of the RLN with the goal of achieving a medialized cord with sufficient bulk to prevent aspiration and to allow apposition of the mucosal edges. There is minimal donor nerve morbidity with this procedure compared with other donor nerves. This may be combined with cord injection simultaneously or with open thyroplasty/arytenoid adduction at a later time. (see below) While these procedures are not likely to restore normal functional mobility to a transected nerve, they may provide muscular tone to the vocal fold that may enhance voice quality and potentially prevent aspiration. It is recommended that this repair be performed within 24 months following injury [40].

There may be an occasion where the surgeon is faced with an intraoperative iatrogenic transection injury. The options for management of transection include primary neurorrhaphy or cross innervations as described above. In addition, injection thyroplasty may be performed simultaneously with or in place of an attempted neural repair. With this technique, an injection is made just lateral to the vocal process of the affected arytenoid cartilage in order to medialize the immobile vocal cord. Slight overinjection may be advantageous as some resorption may be expected with time. Of course, caution is advised to avoid compromise of the airway. Various substances have been used and most have temporary effect which can last 3–6 months. Common substances now include autologous fat, collagen, gelfoam, and hydroxyl appetite [41–43]. Teflon had been used in the past with more durable effect, but was associated with laryngeal granuloma that could cause airway compromise and so has been largely abandoned [44].

Recovery

Overall, it has been shown that recovery can be seen in up to 40% of patients sustaining vocal cord immobility after thyroid surgery [8]. Recovery of vocal fold immobility may be expected to occur over the first 6 months following injury in 80% of cases where it will recover [45]. Recovery is more likely after surgery for benign disease [46] and when the nerve was identified [47]. Treatment may include steroids for transient, mild RLN injury. Lore has found that rates of temporary immobility are much lower (9.1 versus 2.6%) with the use of perioperative steroids [48].

As discussed below, management of a permanent RLN paralysis may challenge the thyroid surgeon or laryngologist postoperatively. Vocal fold immobility that lasts more than 6 months may be considered permanent. These patients would temporarily benefit from injection procedures mentioned above and might potentially be considered for reinnervation. However, most laryngologists would likely opt for a long-term but static medialization procedure such as the open thyroplasty (Isshiki thyroplasty). This is the state of the art static procedure for paralytic dysphonia that involves creating a window in the thyroid cartilage and bolstering the true vocal fold in a medial position to enhance cord apposition with the contralateral mobile cord. This procedure had been performed in the past with sculpted silicone shims [49, 50], but more recently has been successfully completed with Gore-Tex implants [51]. This procedure may be performed under local or general anesthesia. If done under local anesthesia, patient vocalization can help guide the surgeon's efforts. Arytenoid adduction can be combined with medialization laryngoplasty especially when the affected cord is lower than

the normal cord for optimum vocal strength and range [52].

Voice Changes with Thyroid and Parathyroid Surgery

Perhaps since the time of Kocher, who was awarded the Nobel Prize in medicine for his refinements in the technique of thyroid surgery, attention has been focused on the minimization of operative morbidity. The major morbidity associated with thyroidectomy remains paralytic dysphonia. While symptomatic presentation in these instances is often clear, there are cases that are not so evident despite complete vocal fold immobility. Even more difficult are incomplete limitations in cord movement. The resultant vocal changes associated with these injuries are not always simple to predict or even to accurately describe clinically. Close examination in recent years has shown that the changes resulting from RLN injury may be variable and, in addition, other lesions can lead to alterations in voice even in the absence of RLN paralysis. It is only recently that we have recourse to the advanced techniques of laryngology and voice analysis that enable us to record, study, correlate, and understand the many vocal consequences of thyroid surgery (See Table 14.3).

Neural Injury

The presentation of RLN and EBSLN injury has been discussed in more detail above. The clinician may notice clues to underlying voice problems prior to more formal evaluation by noting the patient's respiratory pattern and speaking voice. Dyspnea and stridor in the early postoperative period may be signs of bilateral vocal lesions while a "breathy" voice due to air escape during phonation, vocal fatigue, and lack of projection may indicate a unilateral RLN injury. Limited vocal range and pitch can be a reflection of SLN injury and malfunction of the cricothyroid muscle and perhaps laryngeal framework [53].

Non-Neural Laryngeal Injury

Like neural injuries, non-neural injuries may be due to the extent of patient disease or may be iatrogenic. Benign or malignant thyroid tumors and associated inflammatory conditions may affect the endolarynx as well as the laryngeal skeleton and musculature in addition to the laryngeal nerves. It is now believed that many of the changes in the voice after thyroid surgery arise from changes that are non-neural in nature.

It has been shown that intubation alone may affect the postoperative voice temporarily and even permanently in very rare cases. Vocal cord edema and posterior granuloma due to intubation trauma are relatively rare but recognized risks of general anesthetic with intubation. These may be responsible for temporary changes in voice whereas injuries such as arytenoid dislocation may cause permanent dysphonia. Voice changes may be seen in 5% of patients after intubation alone [54].

Some have suggested that it is a change in the laryngeal mechanics created by a disruption of the extralaryngeal framework (e.g., strap muscles) that is responsible for dysphonia. Hong and Kim evaluated vocal function in 54 patients and found that even in the absence of RLN or EBSLN injury, patients experienced vocal fatigue as well as changes in the speaking and singing voice. Indeed, acoustic analysis revealed changes in the speaking fundamental frequency, range of speaking fundamental frequency, and vocal range after surgery [55]. Soylu et al. prospectively studied 48 consecutive patients who had undergone thyroidectomy without reported nerve injury [56]. The acoustic voice analysis was performed preoperatively, on the second postoperative day, and 3 months after the operation. All patients in the study had demonstrable deficits on the test battery. A significant minority of patients (37.5%) complained of subjective voice changes in the early postoperative period. Those who did not remained symptom free throughout the study period. Only 14.6% had symptom complaints that failed to resolve by 3 months and these patients demonstrated changes in the mean vocal fundamental frequency (F_0) only. Lombardi prosepectively examined 39 patients for voice and swallowing changes following total thyroidectomy using techniques

including video strobolaryngoscopy and acoustic voice analysis preoperatively as well as at 1 week, 1 month, and 3 months postoperatively, and discovered in this patient population without any nerve injuries, mild change in voice and swallowing were experienced by a majority of patients after total thyroidectomy. While these changes reached the level of statistical significance, most had resolved by 3 months postoperatively [57]. Musholt and Musholt studied over 130 patients undergoing thyroid and parathyroid surgery in a prospective four-arm study of changes in the speaking and singing voice postoperatively. They found that in the more extended procedures, the highest pitch of the singing voice decreased significantly, especially in women. Changes in speaking voice remained subclinical [58]. Although the mechanism of postthyroidectomy voice disturbance in patients with preserved nerve function is not yet fully understood, it appears to be temporary and may be attributed to surgical trauma, laryngotracheal fixation of the prelaryngeal strap muscles, or trauma to the arytenoids, e.g., during intubation [56, 57]. As these injuries are often more difficult to identify than neural injuries and their mechanisms have yet to be completely elucidated, often little more than voice rehabilitation with a speech pathologist is offered as treatment.

Voice Evaluation

When there is concern on the part of the patient or the surgeon that a pertinent dysphonia exists, it must be evaluated in an objective manner. There are a number of clinical tools that may be used during this evaluation.

Laryngoscopy

As stated above, the larynx must be evaluated preoperatively and postoperatively in order to accurately understand the effects of thyroid disease and surgery upon the larynx. The appearance of the larynx should be symmetrical at rest and in phonation. With vocal cord paralysis, the vocal folds may not meet in the midline upon volitional adduction, and the affected cord will usually remain lateralized in a paramedian or fully abducted position. The true vocal fold often appears in a bowed state and the arytenoid often will be displaced anteriorly giving the cord a shortened appearance. Laryngoscopy has been shown to be highly sensitive in diagnosing vocal movement abnormalities due to RLN injury [3].

Stroboscopy

Stroboscopy is a technique, often performed by a voice specialist or laryngologist, that allows observation of the anatomic and functional (vibratory) behavior of the vocal cords in the awake patient during a brief office procedure. The mucosal wave is responsible for vocalization and involves the three-dimensional movement of the superficial epithelial layer of the vocal fold over the deeper lamina propria [1]. The strobe employs a flashing light at a frequency that is set based upon, but varying slightly from, the patient's fundamental vocal frequency. This allows examination of the mucosal wave through its entire cycle rather than obtaining a repeating snapshot of the same point in the phonatory cycle. It has greatly enabled the laryngologist to better understand, diagnose, and treat a variety of vocal cord pathologies including partial and complete vocal immobility.

Video stroboscopy may pick up the mechanical defects in cord function associated with dysphonia and can confirm vocal fold movement deficits when present. A recent study has suggested that this test is 100% sensitive and specific in diagnosing vocal fold abnormalities after thyroid surgery [59]. However, this would not be a cost-effective method for vocal evaluation for all patients, especially when compared with indirect laryngoscopy. Its utility would be realized, however, in those symptomatic patients manifesting with persistent clinical evidence of dysphonia before and after undergoing treatment.

Laryngeal Electromyography

Laryngeal electromyography (LEMG) is a potentially objective means for the evaluation of laryngeal function both before and after surgery. In this technique, electrodes are placed in various laryngeal muscles (most commonly thyroarytenoid, posterior cricoarytenoid, and

cricothyroid) to detect depolarizations evoked by neural stimulation. Three basic patterns emerge, including normal, neuropathy, and myopathy. This test can best differentiate between nerve injury and other mechanical causes of vocal fold dysfunction such as myopathy or fixation of the cricoarytenoid joint. It may also help differentiate cases of partial from complete paralysis. For example, in cases of partial injuries, a pattern marked by decreased amplitude of LEMG responses and delayed latency of response is seen [60]. Decreased evoked potentials, decreased recruitment, longer latency, and lower amplitude responses are frequently seen in neuropathic injuries. In the most severe neuropathic injuries (transection), no spontaneous or evoked potentials are observed and one sees fibrillation potentials and sharp waves on LEMG and evoked LEMG [60]. While exact patterns may vary, it is generally agreed that findings of decreased recruitment, polyphasic waveform morphology, altered motor unit action potential amplitude, spontaneous activity, and evidence of synkinesis are reliable indicators of neuropathy [61]. The reader is referred to an excellent review of the technical aspects and clinical applications of this electrophysiologic test [62].

Studies to determine if LEMG can be used to prognosticate recovery postoperatively are based upon electromyographic studies of facial nerve injuries. Munin et al. evaluated a series of 31 patients who had symptomatic vocal cord immobility and determined that LEMG could correctly predict recovery of function in 66.7% of patients who had a negative test (i.e., excellent prognosis). Positive LEMG results (i.e., fair or poor prognosis) correctly predicted the failure of recovery in 80% of patients [63]. LEMG results are most useful during the 6 months after injury. Afterwards, they may be misleading [35, 64, 65]. Therefore, LEMG data may direct intervention in the first 6 months, e.g., cases of suspected transection with no response or fibrillation by LEMG. Otherwise, it is the opinion of the senior author that intervention for immobile vocal fold should be considered if no signs of recovery are present at 6 months [8]. Action may be taken sooner in cases of definite transection or in symptomatic patients, e.g., with aspiration or marked dyspnea.

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Section II
Parathyroid

15

Embryology, Anatomy, and Physiology of the Parathyroid Glands

Johnathan G.H. Hubbard

Introduction

The parathyroid glands were first dissected and described in the Indian Rhinoceros by Richard Owen from an animal that died in the London Zoological Gardens in 1850. This specimen can still be viewed in the Hunterian Museum at the Royal College of Surgeons in London. The Swedish anatomist and medical student Sandstrom subsequently described and named the glands in 1880.

There are usually four Parathyroid glands close to the thyroid gland whose combined weight is approximately 240 mg. They are yellow/brown in color and roughly the size of a lentil. They can become significantly enlarged in pathological conditions such as primary hyperparathyroidism (HPT) (Fig. 15.1).

Embryology

Mesodermal condensations develop in the primitive pharynx of the human embryo to form branchial arches in the 4th to 5th week of development [1]. These arches are separated by clefts or pouches. The parathyroid glands develop from the endoderm of the third and fourth pouches. The fifth pouch, from which the ultimobranchial body is derived is atypical. It shares a common entrance to the pharynx with the fourth pouch and is usually considered as part of the fourth pouch [1].

Inferior Parathyroid

The inferior parathyroid (PIII) develops from the dorsal aspect of the third pouch while the thymus develops from the ventral aspect. They separate from the pharynx, and the thymus descends caudally pulling PIII with it. The thymus descends to the thorax where it joins with the contra lateral thymus to form the bilobed thymus gland. The tail portions become thin and remain in the neck near the inferior pole of the thyroid or may break up into fragments. PIII is classically located at or posterior to the inferior pole of the thyroid but is commonly found within the thymic capsule in the neck or upper mediastinum. PIII can be ectopically located at any point on its path of descent (Fig. 15.2). Rarely PIII is found cranial to the superior pole of the thyroid, in the carotid sheath, or very rarely around the heart or the aortopulmonary window.

The Superior Parathyroid

The superior parathyroid (PIV) derives from the dorsal aspect of the fourth pouch and descends attached to the thyroid and is classically located on the dorsal aspect of the thyroid frequently beneath the capsule of the thyroid, within a 1 cm radius of the junction of the inferior thyroid artery and recurrent laryngeal

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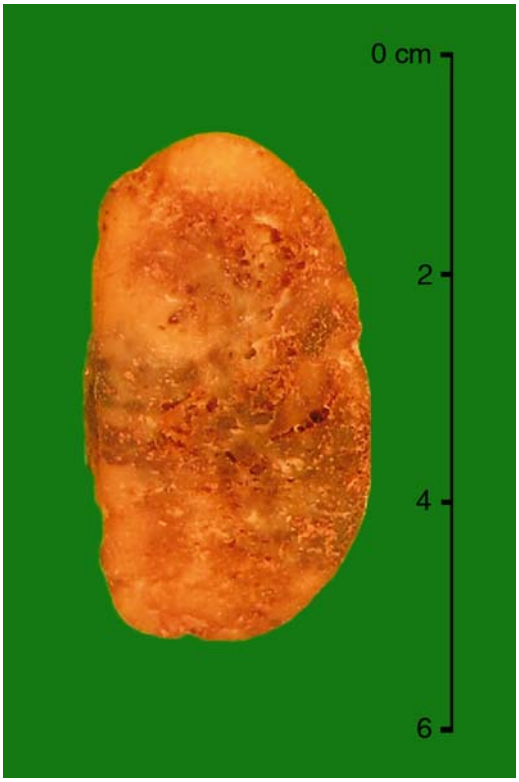

Fig. 15.1. 12.5-g parathyroid adenoma.

nerve (RLN) [2]. Due to the more limited pathway of descent of PIV glands, the ectopic locations are less numerous than with PIII (Fig. 15.2). PIV can be located cranial to the superior pole of the thyroid, in the para or retro oesophageal space, or very rarely be totally intrathyroidal. The ultimobranchial body, derived from the fourth pouch, descends with PIV and gives rise to the parafollicular cells of the thyroid which have neural crest origin and produce calcitonin. These cells become embedded in the thyroid, often leaving a small nodule within the thyroid at its posterior medial aspect, the Tubercle of Zuckerkandl. This can be a guide to the RLN which passes beneath and medially to it, with PIV frequently situated in close proximity.

The upper and lower parathyroid glands take their blood supply from the inferior thyroid artery in most situations although when ectopically placed the superior thyroid artery or thyroid ima artery may be the arterial supply. A capsular plane of dissection when performing a thyroidectomy (Fig. 15.3) helps preserve the parathyroid glands with their blood supply, although some parathyroid glands take vessels direct from the thyroid capsule without an obviously identifiable main feeding vessel [16] and may require autotransplantion to the sternocleidomastoid muscle.

Surgical Aspects

In the adult, PIII is typically located on a plane anterior and medial to the RLN while PIV is located posterior to this plane. As an adenoma develops, the plane of descent of PIV is frequently posterior and caudally toward the mediastinum and it may lie at the same level as PIII but in the posterior plane. Parathyroid localization techniques are therefore important in planning focused (MIV) surgical techniques.

Cadaveric studies have shown that 13% of individuals may have either true supernumerary parathyroid glands (5%) or additional tiny rests of parathyroid tissue that do not amount to a full parathyroid gland (8%) [3]. This is important in planning surgery for patients with conditions where diffuse stimulation of the parathyroid tissue occurs such as secondary HPT or primary HPT in MEN1. In these patients, resection of the cervical thymus and fatty tissue in the central compartment of the neck is important to remove the rest of parathyroid tissue and reduce the risk of persistent or early recurrent HPT.

Calcium Physiology

The vast majority of calcium in the body is stored in bone as hydroxylapatite, and only 1% of calcium is present in the extracellular fluid. Half of serum calcium is in the ionized form (Ca^{2+}). The remaining 50% is metabolically inactive and bound to albumin (40%) or complexed with anions such as phosphate and citrate (10%). Therefore, total calcium levels in plasma are affected by changes in protein concentration, but Ca^{2+} is unaffected. The ionized calcium level is controlled by the hormones PTH and 1,25-dihydroxycholecalciferol (DHCC) and involves regulation of calcium exchange across the gut, the bone, and renal tubule mediated via the calcium-sensing receptor (CaSR).

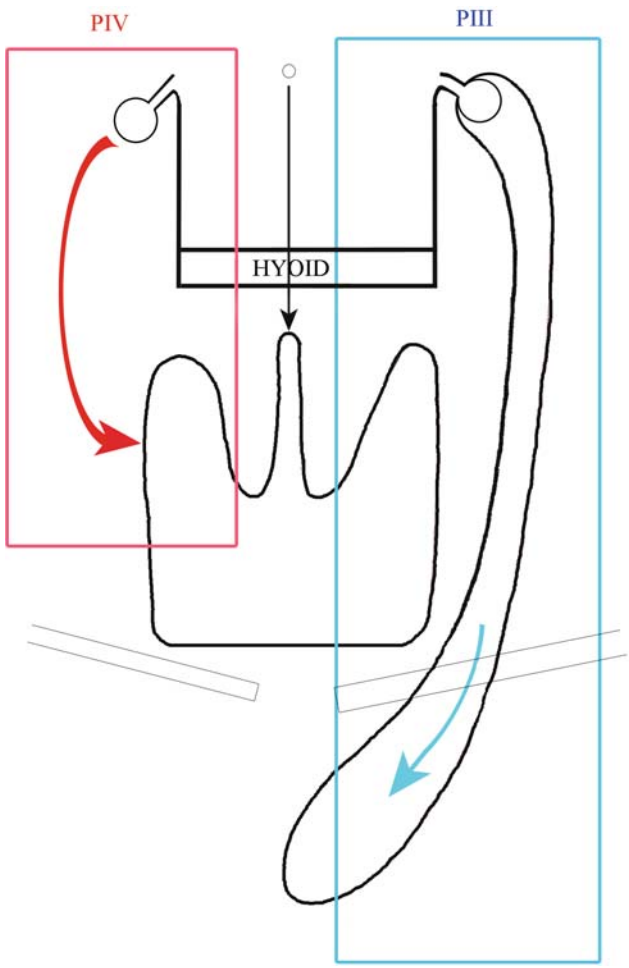

Fig. 15.2. Pathways of descent of PIII and PIV showing area of ectopic locations.

Fig. 15.3. Plane of capsular dissection.

Table 1. Summary of actions of PTH, VIT D and Calcitonin on calcium homeostasis

	PTH	Vitamin D	Calcitonin
Gastrointestinal	Indirect effect via production Vitamin D	Increased calcium/ phosphate absorption	No effect
Bone	Increases osteoclast resorption	Increases osteoclast resorption	Inhibits resorption
Renal	Stimulates resorption – fine tunes calcium uptake in DCT. Inhibits Phosphate uptake PCT	No effect	Inhibits calcium and phosphate resorption

Calcium-sensing receptor (CaSR) (Table 15.1). The commonest causes of persistent hypercalcaemia are parathyroid dysfunction and malignancy (Table 15.2).

Table 2. Some causes of Hypercalcaemia

Malignancy

Primary – multiple myeloma, lymphoma

Secondary with bone metastases

Endocrine

Pheochromocytoma, Thyrotoxicosis, Addisons, Hyperparathyroidism

Familial Hypercalciuric hypercalcaemia(FHH)

Granulomatous disease

Sarcoid, Tuberculosis

Medication related

Lithium, Thiazide diuretics, Vitamin D, Vitamin A

Miscellaneous

Milk-Alkali syndrome, Pagets and immobilisation

Parathyroid Hormone

The endocrine function of parathyroid glands has been recognized for many years. In 1925, parathyroid extract was shown to prevent hypocalcemia in dogs that had undergone parathyroidectomy [4]. PTH is an 84 amino acid (aa) peptide synthesized by the chief cells of the parathyroid gland. Its gene is located on chromosome 11. It is secreted in a prepro-PTH form. The presequence (23aa) and prosequence (6aa) are removed by the endoplasmic reticulum and Golgi apparatus before PTH is packaged into secretory granules for secretion [5].

Intact (1–84aa) PTH has a half life of 2–4 min and is broken down by the liver and kidney yielding amino and carboxy terminal fragments. Carboxy terminal fragments are excreted via the kidney and accumulate in renal failure. Early radioimmunoassays to measure PTH were developed in the 1960s [6] however interpretation of results was problematic as breakdown fragments of PTH were detected. Current PTH assays measure intact PTH with either a two-site immunoradiometric assay (IRMA) or immunochemiluminescent assay (ICMA). In the late 1980s, alteration of the incubation times and temperatures reduced assay times (15 min) and enabled the quick measurement of PTH, which is today frequently used to monitor adequacy of excision during focused techniques of parathyroidectomy.

The main function of PTH is to control Ca^{2+}. PTH acts via the receptors, PTH-1, and PTH-2. The first 34 amino acids are responsible for the biologic effects of PTH. Amino acids 18–34 bind the receptor with amino acids 1–6 required for its activation. PTH-related peptide (PTHrP) secreted by malignant tumurs produces hypercalcemia by activating the PTH-1 receptor [5].

The kidneys filter large amounts of calcium (~10 g/day). The majority (60–70%) is reabsorbed in the proximal tubule and thick ascending limb of Henle by passive paracellular absorption. PTH stimulates reabsorption of calcium in the kidney and is particularly important for fine tuning calcium active uptake in the distal convoluted tubule. Active uptake of Ca^{2+} occurs via the epithelial Ca^{2+} channel TRPV5 (transient receptor potential vanilloid-5) on the luminal side of the distal convoluted tubule (DCT) and is the rate-limiting step in transcellular calcium reabsorption. New regulators currently under investigation that are implicated in the regulation of renal calcium uptake via TRPV5 expression include 1,25-DHCC, estrogen, tissue kallikrein, and klotho (an anti aging protein)[7].

PTH indirectly stimulates gut uptake of calcium by stimulating renal production of active vitamin D (1,25-DHCC). Absorption of calcium

occurs throughout the small and large intestine with maximum absorption occurring in the duodenum and jejunum, via active and passive means. Active uptake is regulated via the epithelial Ca^{2+} channel, TRPV6 [7].

PTH activates osteoclasts causing bone resorption and elevation of serum calcium but in the longer term also stimulates new bone formation.

In the kidney, PTH has a marked phosphaturic effect by inhibiting the reabsorption of phosphate in the proximal convoluted tubule. In renal failure, GFR is reduced and phosphate is retained, both factors are reported to induce fibroblast growth factor 23 (FGF23) [7, 8, 9]. FGF23 is a bone-derived circulating factor that has an important role in phosphate and vitamin D regulation. FGF23 inhibits phosphate reabsorption in the kidney and inhibits the production of vitamin D. PTH levels rise secondary to reduced vitamin D levels and possibly as a direct consequence of raised levels of FGF23. Retained phosphate complexes with calcium and contributes to the hypocalcemia of renal failure, which further stimulates the production of PTH by the parathyroid glands.

Vitamin D

Vitamin D is obtained from the diet and is formed in the epidermis of the skin with exposure to adequate sunlight. It is metabolized in the liver to 25-hydroxycholecalciferol (HCC) and further in the kidney. The main active form is 1,25-DHCC, produced via the action of the 1α–hydroxylase enzyme on 25-HCC in the kidney. The actions of vitamin D are mediated via the nuclear vitamin D receptor (VDR). Production of 1,25-DHCC is stimulated by PTH, IGF-1, and is inhibited by high levels of calcium, phosphate, and FGF23. Vitamin D has an important role in regulating calcium homeostasis with PTH, particularly the gut absorption of calcium and in regulating bone formation particularly bone resorption mediated by osteoclasts.

The Calcium Sensing Receptor

The calcium sensing receptor (CaSR) was cloned in 1993[10]. The CaSR is a 1078aa cell surface protein and member of the G-protein-coupled receptor family. The CaSR gene is located on chromosome 3 (3q13.3–21). The CaSR is widely found throughout the body including the parathyroid glands, C cells of the thyroid, kidney, intestine, bone, and brain. The CaSR enables the parathyroid glands to sense Ca^{2+} levels and adjust the amount of parathyroid hormone secreted. There is negative feedback between Ca^{2+} and PTH. The steep section of the sigmoid relationship lies within the normal range of serum Ca^{2+}, such that there is an inverse relationship between PTH and serum Ca^{2+} within this range [11].

High levels of calcium activate the CaSR resulting in a suppression of PTH levels, while low levels of calcium inactivate the CaSR resulting in high levels of PTH. The mechanism by which this occurs remains poorly understood and under investigation [12].

Calcitonin

The CaSRs in the C cells of the thyroid are set up in an opposite fashion to those in the parathyroid glands, such that activation with calcium results in secretion of calcitonin which lowers calcium and inactivation due to low levels of calcium suppresses calcitonin secretion. Calcitonin is a 32aa peptide coded by the CALC-1 gene. Calcitonin inhibits osteoclast activity in bone and inhibits reabsorption of phosphate in the kidney and increases renal excretion of calcium. Although it has actions to lower serum calcium, calcitonin is relatively unimportant as an acute regulator of calcium homeostasis in humans as demonstrated by the lack of complications following total thyroidectomy. It is an important tumor marker in MTC.

Genetic mutations of the CaSR have been linked with clinical disorders such as familial hypocalciuric hypercalcemia (FHH) and neonatal severe HPT. FHH is rare and caused by a heterozygous inactivating mutation of the CaSR. This autosomal dominant disorder is characterized by hypercalcemia with low urinary calcium excretion. The calcium clearance to creatinine clearance ratio (CCCR) is $<$0.01.Typically, individuals have a normal (inappropriate) PTH and mild hypermagnesemia. These patients do not benefit from

parathyroidectomy and the clinical importance is to differentiate FHH from other forms of HPT that benefit from surgery. Screening involves measuring the CCCR and performing CaSR gene analysis when CCCR is <0.02 [13].

Drug Modulators in Parathyroid Disease

Type II calcimimetics drugs (e.g., cinacalcet hydrochloride) are positive allosteric modulators of the CaSR which enhance the sensitivity of the receptor to calcium resulting in a decrease in PTH secretion [12, 14]. Cinacalcet hydrochloride has therapeutic use in patients with SHPT and is often used in conjunction with selective VDR agonists [14], e.g., paricalcitol. Selective VDR agonists reduce PTH levels in SHPT patients without the rise in serum calcium and phosphate seen with calcitriol with the benefit of reducing vascular calcification and complications seen in SHPT [15].

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16

Presentation and Diagnosis of Primary Hyperparathyroidism

Jenny Gough and F. Fausto Palazzo

Introduction

The term hyperparathyroidism was first coined in the 1920s to describe a syndrome characterized by bone disease, renal stones, fatigue, hypercalcemia, and hypercalciuria [1]. The diagnosis was dependent on symptoms related to "bones, stones, abdominal groans and moans" which often correlated with osteitis fibrosa cystica, advanced kidney disease, psychiatric, and neuromuscular disorders, respectively. The clinical features were often associated with radiological evidence of subperiosteal erosion of the phalanges, brown tumors, and salt and pepper erosions on the skull radiograph (Figs. 16.1 and 16.2). With Rasmussen and Craig's isolation and characterization of parathyroid hormone (PTH) in 1959 and Berson and Yalow's development of an immunoassay for PTH in 1963 [1] our understanding of calcium metabolism and the definition of primary hyperparathyroidism(pHPT) improved. It is appropriate that the definition, like the current commonest presentation of pHPT, is biochemical: hypercalcemia in the presence of an unsuppressed and therefore relative or absolute inappropriately elevated PTH level. The disease now covers a spectrum that has extremes as diverse as asymptomatic normocalcemic hyperparathyroidism and hypercalcemic crises.

The arrival of the multichannel-automated serum electrolyte analysis machine in the 1970s made symptoms no longer a prerequisite for the diagnosis of pHPT. The routine measurement of serum calcium unearthed a large number of previously unrecognized patients with hypercalcemia. Since pHPT is the commonest cause of hypercalcemia in the community [2], the prevalence of pHPT, or rather the prevalence of its diagnosis, increased in parallel, resulting in a fivefold increase in the incidence of pHPT [3]. In North America, the incidence of pHPT is now 4.3/1000 per annum [4] with an estimated 100,000 new cases diagnosed each year in the USA alone [5]. The incidence across Europe is thought to be 3/1000 [6], although a Swedish population-based study suggests the prevalence of pHPT rises to 2.1% of postmenopausal women aged 55–75 [7] or to 3.4% for those aged 65–84 [8]. Overall, the incidence of pHPT is twice as high in females as in males and increases with advancing age in both sexes [6].

Most patients with pHPT present sporadically with no apparent risk factors. The known risk factors for pHPT include radiation exposure [9], long-term lithium use [10], and a family history of hyperparathyroidism [11] or multiple endocrine neoplasia syndromes (MEN1 and MEN2A). Parathyroid disease in MEN1 is usually multiglandular and occurs in 95% of patients making pHPT the major feature of the syndrome [12]. In patients with MEN2A, hyperparathyroidism is a less common component of the syndrome, is less frequently multiglandular, and is usually a milder disease than in MEN1 [13].

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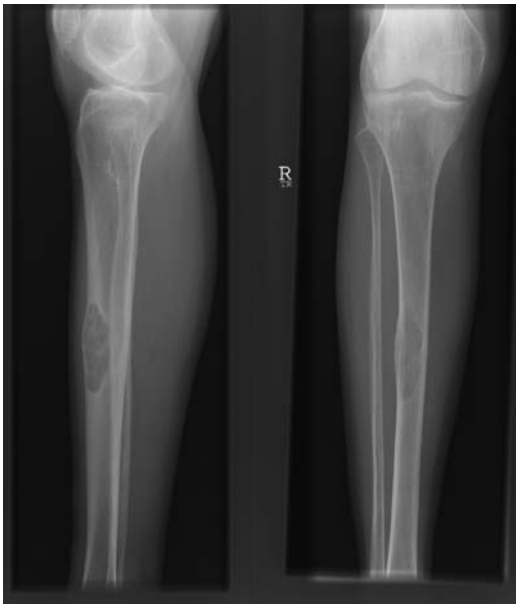


Fig. 16.1. Browns tumor of tibia due to hyperparathyroidism.

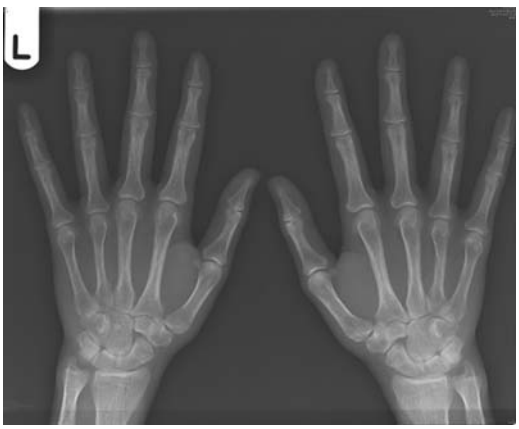


Fig. 16.2. Subperiosteal bone erosion of proximal phalanges and metacarpals in hyperparathyroidism.

Clinical Features

Primary hyperparathyroidism in its classic symptomatic form, with severe skeletal and renal complications and in extreme cases mortality, is today seen only in patients in or from developing countries [14]. Elsewhere, the disease is most commonly diagnosed following the investigation of an incidentally identified hypercalcemia, usually in an apparently asymptomatic patient [5]. A small proportion of patients may have traditional symptoms including renal calculi [15] and pancreatitis [16]. Less common presentations include recurrent miscarriages and neonatal tetany in an undiagnosed hypercalcemic mother [17]. Primary hyperparathyroidism may also be detected by focussed screening programs in patients known to carry the MEN1, MEN2A, or HRPT2 genes or to be directly related to a gene carrier.

"Asymptomatic" Primary Hyperparathyroidism

Whilst most patients currently diagnosed with pHPT are described as asymptomatic [5], this refers to the absence of the overt clinic symptoms of advanced parathyroid disease. If the myriad of subtle clinical symptoms such as malaise, fatigue, depression, memory loss, poor concentration, polydipsia, polyuria, constipation, and nonspecific bone and joint aches are taken into consideration, the incidence of truly asymptomatic disease may be lower than 5%, with no correlation between degree of hypercalcemia and the extent of these symptoms [18] (Table 16.1).

Health-related quality of life scores such as SF36 (Medical Outcomes Study Short-Form Health Survey) [19] are reduced in asymptomatic patients [20] and they improve following parathyroidectomy [21]. Pasieka has designed a disease-specific visual analog questionnaire to quantify the subtle symptoms of pHPT, the *P*arathyroidectomy *A*ssessment of *S*ymptoms (PAS) score (Table 16.2). The higher the PAS score the more symptomatic the patient. This assessment tool has been validated by comparing the pre- and postoperative scores of patients with pHPT and control patients undergoing surgery for euthyroid thyroid disease [22]. Quality of life assessed with this tool improved following parathyroidectomy, with high preoperative PAS scores which decreased significantly postoperatively compared to controls. The validity of the PAS scoring system is further supported by the fact that it also correlates with SF-36 scores in patients undergoing parathyroidectomy for pHPT [23]. The consistent improvements in PAS and SF-36 scores following parathyroidectomy underline the tenuous nature of the "asymptomatic" label attached to many of such patients [24, 25].

Table 16.1. Symptoms and signs of primary hyperparathyroidism

Musculoskeletal	Renal	Neuropsychiatric
Muscle weakness	Renal calculi/renal colic	Impaired concentration
Myalgia	Nephrocalcinosis	Memory loss
Bone aches/pains	Thirst/dehydration	Anxiety
Osteoporosis	Polyuria/oliguria/anuria	Depression
Osteitis fibrosa cystica	Renal failure	Confusion
Brown's tumors		Dementia/paranoia
		Ataxia
		Hyporeflexia
		Coma
Gastrointestinal	**Cardiovascular**	**Other**
Nausea/vomiting	Hypertension	Visual changes
Abdominal pain	Vascular calcification	Band keratopathy (corneal calcification)
Anorexia	Shortened Q-T interval	Conjunctivitis
Peptic ulcer disease	Bradycardia	Pruritus
Pancreatitis	Heart block	
Constipation	Lethal arrhythmias	
Weight loss		

Table 16.2. Pasieka's parathyroidectomy assessment of symptoms (PAS) score [19]

Symptoms	Not experiencing the symptom 0	Experiencing the most extreme aspect of the symptom 100
Pain in the bones		
Feeling tired easily		
Mood swings		
Feeling "blue" or depressed		
Pain in the abdomen		
Feeling weak		
Feeling irritable		
Pain in the joints		
Being forgetful		
Difficulty getting out of a chair or car		
Headaches		
Itchy skin		
Being thirsty		

Even if patients have what may be considered asymptomatic or paucisymtomatic disease, pHPT is clearly not innocuous. Various studies have demonstrated higher rates of hypertension, dyslipidemia, insulin resistance, unfavorable body fat distribution [26], cardiac and vascular dysfunction, and morbidity from cardiovascular diseases in patients with mild pHPT [27]. Twenty-five-year follow up of pHPT patients with untreated hypercalcemia demonstrates an excess number of premature cardiovascular deaths compared to age-matched normocalcemic controls [28]. In addition to increased cardiovascular morbidity, decreased bone mineral density (BMD)

has been reported in patients with mild or "asymptomatic" pHPT, and both appear to normalize after parathyroidectomy [27]. Five years following parathyroidectomy, a Swedish population study demonstrated increased BMD in L2–L4 to the level of matched controls, increased femoral neck BMD in patients <67 years of age, and preservation of femoral neck BMD in the elderly population [29]. There is also evidence of improvement in dyslipidemia [30] and glucose tolerance [31] following surgery, which may explain the improvement in cardiovascular morbidity. Retrospective data seem to indicate that early surgery for mild pHPT normalizes cardiovascular risk and offers a survival advantage, but long-term follow-up is required to either prove or disprove this. A randomized, controlled trial of 191 patients has compared the morbidity and quality of life of parathyroidectomy and medical observation in mild asymptomatic pHPT. Asymptomatic patients with mild pHPT have decreased quality of life and more psychological symptoms than normal controls. However, at 2-year follow up a benefit of operative treatment, compared with medical observation, has not yet been proven utilizing these parameters [32].

Symptomatic Primary Hyperparathyroidism

Amongst patients with unequivocally symptomatic disease, nephrolithiasis is the commonest clinical feature [33]. Renal stones and ureteric colic are significantly more frequent in younger patients where hypercalciuria is commoner due to the higher levels of active vitamin D [15]. However, nephrolithiasis may also occur in the absence of symptoms, thus justifying ultrasonographic renal assessment in patients with proven pHPT.

Bone disease culminating in pathological fractures in pHPT is now uncommon, indeed the earlier data suggesting increased fracture risk [34] has not been supported by the outcomes of more recent studies [35, 36]. One study even suggested that the increase in bone turnover in mild pHPT protected against the loss of cancellous bone structure that normally follows menopause [37]. These data, however, do not correlate entirely with the more recent large study that demonstrates parathyroidectomy to be independently associated with a decreased fracture risk in age-matched patients [38]. As bone disease may only present clinically and radiologically at an advanced stage, bone densitometry of cortical bone is therefore required to demonstrate osteoporosis in patients with general aches in the context of pHPT.

Gastrointestinal symptoms resulting from smooth muscle relaxation include constipation, anorexia, nausea, and vomiting. The high incidence of peptic ulcers and abdominal pain from other causes in patients with pHPT has been recognized for many years. Hypercalcemia increases gastric acid secretion and may account for associated ulcer disease and the ulcer-like pain in pHPT. The mechanisms causing the other gastrointestinal symptoms in hypercalcemia remain to be elucidated [39]. The association of pHPT with peptic ulcer disease is variable with series showing no association contrasting with others where as many as 12 of 20 patients with pHPT are affected. Selection bias and the context of the diagnosis is likely to explain these contrasting findings. Of significance, however, is that the majority of patients with abdominal symptoms thought to be secondary to pHPT experience complete resolution of their symptoms following parathyroid surgery [40, 41].

Pancreatitis is believed to be more common in pHPT and directly related to the hypercalcemia of pHPT, but the molecular mechanism by which this occurs remains unknown. In the 1980s, the Mayo clinic audited their patients with pancreatitis in the presence of proven pHPT and found an incidence of 1.5%, which was the same as for patients without pHPT [42]. The natural and often quoted conclusion was that there was no direct causal correlation between the two diseases. However, once again selection bias is the likely culprit for this finding since the patients involved in this series all had asymptomatic and/or mild pHPT. Indeed, subsequent studies from Australia, Germany, and France have all demonstrated an increased prevalence of pancreatitis in patients with pHPT – 5.1, 5.6, and 3.2%, respectively [43, 16, 44]. Furthermore, a study from India, where pHPT is still seen in its more florid form with more marked hypercalcemia, demonstrated an incidence of up to 8% [16].

The effects of pHPT on the cardiovascular system include hypertension, vascular calcification, shortened Q-T interval, and arrhythmias [45]. Whilst subtle neurological symptoms are common, severe manifestations such as confusion, hypotonia, muscle weakness, and coma are present only in hypercalcemic crises (vide infra).

Clinical examination of patients with pHPT is usually unremarkable and serves to exclude pathologies that represent an alternative cause of hypercalcemia. Corneal calcification may be present but may equally be an unrelated coexistent feature.

Hypercalcemic Crisis

A hypercalcemic crisis is an uncommon condition that occurs in no more than 1–2% of pHPT [46]. It is characterized by a serum calcium greater than 3.5 mmol/l (14 mg/dl) and is typically associated with a rapid deterioration in central nervous system, cardiac, gastrointestinal, and renal function. The majority of cases are due to pHPT and are therefore also known as parathyrotoxic crises. The hypercalcemia of advanced malignancy whilst being the next most frequent cause of severe hypercalcemia tends to present more indolently [47].

The presentation of the parathyrotoxic crisis may be insidious and initially subtle or overt and acute with confusion, delirium, abdominal pain (sometimes with pancreatitis), vomiting, dehydration and anuria, and occasionally with a palpable parathyroid adenoma in the neck [48]. The severe presentation is a consequence of untreated advanced pHPT combined with dehydration or another condition causing fluid shifts out of the intravascular compartment. Life-threatening arrhythmias may occur due to a prolongation of the Q-R interval and shortening of the Q-T interval. Coma and cardiac arrest are possible in particular when serum calcium levels reach 3.75–4 mmol/l (15–18 mg/dl).

The priority in hypercalcemic crises is prevention rather than cure. This relies on avoiding dehydration by maintaining a fluid intake of 3 L or more a day especially in patients with hypercalcemia greater than 2.8 mmol/l.

If prevention has failed or the serum calcium is >3 mmol/l, admission to hospital for in-patient management is adviseable [49] since hypercalcemic crisis in its acute form represents a medico-surgical emergency. The management strategy focuses on maintaining an adequate airway and breathing, aggressive rehydration aimed at generating calciuresis, whilst also decreasing calcium release from skeletal stores.

The in-patient rehydration should commence with intravenous normal saline titrated to achieve a urine output of 100 ml/h. Following adequate rehydration, loop diuretics may be introduced to stimulate both calciuresis, and these drugs present the additional advantage of inducing diuresis, thus preventing fluid overload. The frequently coexisting cardiac and renal comorbidities in these patients make an appropriate monitoring environment (i.e., high dependency or intensive care unit), essential and regular serum electrolyte estimation is required to prevent electrolyte imbalances, in particular hypokalemia and hypomagnesemia. Usually, serum calcium levels can be reduced by 1.6–2.5 mg/dl within 24 h with only rehydration and loop diuretics [50]. However, these measures alone are insufficient to normalize calcium in extreme cases and additional agents alone or in combination may be used to achieve normocalcemia including bisphosphonates, calcitonin, steroids, and dialysis (Table 16.3).

Bisphosphonates are pyrophosphate analogs that have a high affinity for hydroxyapatite in bone. They are potent inhibitors of osteoclast activity and can act for months. In hypercalcemia secondary to malignancy, they are extremely effective normalizing serum calcium in most patients [51]. However, their prolonged action is not favored for the management of patients with pHPT awaiting surgery as a troublesome profound and prolonged hypocalcemia may follow postoperatively. Calcitonin can be used as a temporizing measure until the more sustained effects of other agents begin. It has the advantage of acting within 24–48 h to lower serum calcium levels [52], by increasing calciuresis and decreasing osteoclast activity. The duration of action of calcitonin, however, is limited to a few days and it is most effective when used in combination with steroids [53], although long-term use even in combination is limited by tachyphylaxis and allergic reactions [54]. Glucocorticoids lower serum calcium by several mechanisms including the inhibition of the effects of vitamin D [55], inhibition of osteoclast-activating factor [56], and by decreasing the intestinal absorption and increasing the renal excretion of calcium [57]. However, glucocorticoids are more effective for hypercalcemia from granulomatous disease and malignancy than pHPT and so are rarely used in this context. Another agent, gallium nitrate which inhibits bone resorption, is now also less commonly used due to its nephrotoxicity, the need

Table 16.3. Management of hypercalcemia

Treatment	Onset of action	Duration of action	Mechanism of action	Advantages	Disadvantages	Effectiveness % normalized
Intravenous normal saline	Hours	During use	Increase in calciuria Hemodilution	Rehydration	Fluid overload in congestive heart failure Hypokalemia/ hypomagnesemia	0–10
Loop diuretics						
Frusemide	Hours	2–6 h	20–500 mg/day induces diuresis and calciuria 100 mg/h infusion directly stimulates calciuria	Rapid onset	Electrolyte abnormalities Dehydration Renal impairment	0–10
Bisphosphonates						
Etidronate	1–2 days	5–7 days	Inhibition of osteolysis Antiresorptive	Intermediate onset	Hyperphosphatemia 3-day infusion	30–80 70–100
Pamidronate	1–2 days	10–14 days		High potency Medium duration	Fever (20%) Hypophosphatemia Hypomagnesemia Hypocalcemia (can be profound if parathyroidectomy performed soon after treatment)	
Zoledronic acid	Rapid	20–28 days (twice as long as pamidronate)		Rapid action Long duration	Renal impairment	Unknown, not yet licensed for use
Calcitonin	Hours	2–3 days	Inhibition of osteolysis	Fast onset Used as a bridge until intermediate action drugs take effect	Tachyphylaxis Flushing Nausea/vomiting	10–20
Hemodialysis	Hours	During use	Removal of calcium from blood	Rapid onset Treatment for renal failure	Dialysis complications (catheter related, hypotension)	Very effective if tolerated
Glucocorticoids	5–7 days	Days–weeks	Increase calciuresis Decrease intestinal absorption of calcium	Oral therapy Tumoricidal effect on hematological and breast malignancies	Only effective in vitamin D excess or granulomatous disease Immunosuppression Cushing's syndrome	Variable

for continuous infusion, and lack of clinical data to support its use [50]. Parathyrotoxic patients with renal failure who cannot tolerate large-volume resuscitation may require dialysis with low calcium dialysate, and such a strategy may remove up to 250 mg of calcium/h.

Concurrent investigations should proceed in parallel during the management of the hypercalcemic crisis, and surgical treatment should follow once the patient has been rendered safe. The high mortality associated with hypercalcemic crises appears to have been related to a failure to make the diagnosis and delays in appropriate management. Urgent parathyroidectomy remains the most expedient method of restoring normocalcemia [58] and has minimal morbidity and mortality, with long-term success rates similar to elective parathyroidectomy [59]. In contrast, the hypercalcemic crisis of advanced malignancy implies a very limited life expectancy, often only a matter of weeks, and palliative management is usually appropriate [45].

Normocalcemic Hyperparathyroidism

As parathyrotoxic crises have become a rare occurrence, its place is being taken by a disease that represents the other end of the pHPT spectrum, namely normocalcemic hyperparathyroidism. These patients are normocalcemic but with a consistently inappropriately elevated PTH in the absence of secondary causes of hyperparathyroidism (Table 16.4). The significance of this condition is controversial, but growing evidence suggests that it may represent the earliest form of pHPT, a phase characterized by elevated PTH that leads to a reduced cortical bone density but without hypercalcemia. The second phase of pHPT is defined by the development of hypercalcemia and therefore leads to the investigation and diagnosis.

Normocalcemic pHPT is being increasingly diagnosed in the context of early bone disease due to the increasing awareness of this problem. Indeed many skeletal health physicians consider the measurement of PTH as a part of the routine assessment of decreased bone density [60]. Normocalcemic pHPT is a new disease, being first described by Mather [61] in 1953. He treated a 33-year-old normocalcemic woman with osteitis fibrosa cystica, whose symptoms resolved following removal of a parathyroid adenoma. The true incidence of the condition, however, in the past has been confounded by secondary causes of hyperparathyroidism, mainly vitamin D deficiency [62] and by the inclusion of patients with intermittent hypercalcemia [60]. Vitamin D is a fat soluble substance which is prevalent in dairy products. It is absorbed from the gastrointestinal tract and hydroxylated in the liver to 25-hydroxyvitamin D. Once activated by the kidneys, 1,25-dihydroxyvitamin D increases resorption of phosphorus in the kidneys and absorption of calcium from the gastrointestinal tract. A deficiency of Vitamin D can lead to raised PTH levels in normocalcemic patients and possibly lead to the misdiagnosis of primary hyperparathyroidism.

Where secondary causes of PTH elevation have been excluded, normocalcemic pHPT increasingly probably represents the earliest manifestation of parathyroid autonomy. There is also growing evidence that normocalcemic pHPT, like the hypercalcemic variant, is not truly asymptomatic as previously thought. The classic subtle symptoms and signs typical of pHPT may be present, and one series of 37 patients that were investigated showed that 14% had nephrolithiasis, 57% osteoporosis, and 11% fragility fractures. Over an 8-year of follow up 19% developed hypercalcemia, 5%

Table 16.4. Secondary causes of PTH elevation

Secondary causes of PTH elevation
Chronic renal failure
Vitamin D deficiency
Dietary
Lack of sun exposure
Familial hypocalciuric hypercalcemia
Liver disease
Gastrointestinal malabsorption
Vitamin D and calcium
Medications
Lithium
Thiazide diuretics
Bone disease
Osteoporosis
Osteomalacia
Rickets

marked hypercalciuria, and 29% progressive cortical bone loss [63]. The same group of normocalcemic hyperparathyroid patients also had elevated glucose, serum lipoprotein fractions, and a raised BMI compared to matched controls. Importantly, this metabolic cluster of increased cardiovascular risk factors converged toward the controls group following parathyroidectomy and remained abnormal in those managed conservatively [64].

Nevertheless, the treatment of normocalcemic pHPT remains controversial because the emergence of clinical features of pHPT is unpredictable as is the evolution to a hypercalcemic state. The fact that some patients remain normocalcemic despite the clinical manifestations of pHPT inevitably raises the question of the definition of a "normal" serum calcium level for an individual patient. In other words, is it possible that a serum calcium result within the normal range for the population may represent hypercalcemia for a specific individual?

The symptomatic patients with normocalcemic hyperparathyroidism tend to present with renal calculi and hypercalciuria. Care must be taken in such patients to exclude idiopathic hypercalciuria which is the most common cause of renal calculi, especially problematic since idiopathic hypercalciuria patients may also have raised PTH levels making differentiation of the two conditions difficult. Several tests are useful to distinguish between the two diseases, but none alone is conclusive, thus a combination of two or more are used to make the diagnosis. Thiazide diuretic administration, which decreases urinary calcium excretion, will normalize PTH levels in patients with idiopathic hypercalciuria, but not in those with normocalcemic pHPT [65]. Calcium loading (350–1000 mg orally) results in hypercalcemia and hypercalciuria in those with pHPT, due to increased intestinal absorption [66]. Serum-ionized calcium is often elevated in those with normocalcemia on routine bloods [67] and can also aid in the diagnosis of pHPT.

Differential Diagnosis of Hypercalcemia

The appropriate differential diagnosis of hypercalcemia requires an appropriate understanding of calcium metabolism. Physiologically active serum calcium in the free or ionized form accounts for 50% of total serum calcium. Forty percent of calcium is bound to plasma proteins, (predominantly albumin) and the remaining calcium is complexed to anions including bicarbonate, lactate, phosphate, and citrate. Alterations in serum albumin levels may therefore alter the amount of calcium measured in serum assays, so a calculation is required to establish a calcium level that is "corrected" for this potential confuting variable and that represents a standard against which other calcium values can be reliably measured. Previously, the calculation had to be performed manually but now formulae such as that shown below are automatically performed by the machines used for automated blood sampling although the reference range and therefore the exact formula varies between laboratories [68].

Formula for calculating the calcium level corrected for plasma albumin concentration:

$$\begin{aligned}\text{Corrected Ca} = {} & \text{total Ca (mmol/l)} \\ & + 0.02 \times [40 \\ & - \text{serum albumin (g/l)}]\end{aligned}$$

Calcium homeostasis is tightly regulated by calcium-sensing receptors (CaSRs) in the parathyroid glands that are sensitive to fluctuations in calcium via a negative feedback loop. CaSRs are sensitive to fluctuations in calcium via a negative feedback loop such that under normal circumstances, hypercalcemia inhibits PTH production whereas hypocalcemia inactivates the CaSRs leading to release of the sequestered PTH [69]. CaSRs are also located in the kidneys and gastrointestinal tract, placenta, pancreas, and brain, where they also contribute to calcium homeostasis. In the kidneys, the CaSR regulates renal calcium excretion so that in the presence of a rise in serum calcium, the excess calcium is excreted. In the gastrointestinal tract, the CaSRs are present in the gastrin-secreting G-cells and acid-secreting parietal cells and provide one of the links between hypercalcemia and acid secretion.

The dysfunction of CaSRs is responsible for three uncommon genetically inherited conditions of calcium dysregulation: familial benign hypocalciuric hypercalcemia (FHH), neonatal severe hyperparathyroidism, and autosomal dominant hypercalciuric hypocalcemia (ADHH) which are amongst the important differential diagnoses for disregulation of calcium hemostasis (see below) [70]. An alteration in CaSR

function also lays at the heart of pHPT since in this condition the parathyroid chief cells erroneously interpret the calcium levels as low leading to a lack of inhibition of PTH production and release and therefore hypercalcemia [71]. In vivo studies have confirmed the existence of a calcium-sensing deficit [71], as well as immunohistochemical findings of decreased numbers of CaSRs by 30–70% in parathyroid adenomas [72].

Hypercalcemia is defined as a serum-corrected calcium >1 mg/ml above the normal range (usually 8.5–10.2 or 2.2–2.5 mmol/l) [73]. Whilst hypercalcemia has many causes, the vast majority of patients have either primary hyperparathyroidism or malignancy [53] (Table 16.5). The distinction between pHPT and malignant hypercalcemia is based on the clinical findings – absence of symptoms or signs of malignancy – typically coupled with biochemical findings such as low serum phosphate, normal serum alkaline phosphatase, normal vitamin D, and high 24-h urinary calcium. However, key to ruling out malignancy is the coexistence of an unsuppressed intact PTH (iPTH), indicative of an alteration of the physiological feedback that suppresses PTH release as the serum calcium climbs. The emphasis on iPTH is required to avoid the misleading results that previously occurred due to the cross-reaction with PTH-related protein (PTHrP) secreted by nonparathyroid malignancies although very occasionally iPTH has been reported to be produced by nonparathyroid tumors [74]. In the absence of this exceptional event the presence of hypercalcemia with an unsuppressed iPTH narrows the diagnosis to two conditions: pHPT and familial hypocalciuric hypocalcemia (FHH).

Familial Hypocalciuric Hypercalcemia

Familial hypocalciuric hypercalcemia is an autosomal dominant disorder, with virtually 100% penetrance. It is characterized by hypercalcemia, hypophosphatemia, unusually low renal clearance of calcium, and typically is accompanied by parathyroid hyperplasia [75]. Most cases of FHH are caused by a loss-of-function mutation in the calcium-sensing receptor gene which can now be confirmed on genetic analysis. Typically, patients with FHH have moderate hypercalcemia from an early age but relatively low urinary calcium excretion. PTH levels tend to be normal or mildly elevated but always relatively unsupressed by the patient's hypercalcemia. To exclude FHH it is essential to calculate the calcium/creatinine clearance ratio (below). Failure to exclude FHH can lead to erroneous diagnosis of primary hyperparathyroidism which can lead in turn to one or more unnecessary parathyroid operations.

$$\frac{\text{Urine calcium (mmol/l)} \times [\text{plasma creatinine } (\mu\text{mol/l})/1000]}{\text{Plasma calcium (mmol/l)} \times \text{urine creatinine (mmol/l)}}$$

A ratio <0.01 is diagnostic of FHH and ratios of >0.01 confirm pHPT.

Investigation of Severity Primary Hyperparathyroidism

Once a diagnosis of primary hyperparathyroidism has been confirmed, an assessment of end organ disease should be undertaken including functional and anatomical kidney evaluation and an assessment bone density. These assessments are important since they identify those patients who even in the absence of symptoms have end organ damage and who are therefore most likely to objectively benefit from parathyroidectomy.

Abdominal radiography for the diagnosis of renal and ureteric calculi has been superseded by unenhanced helical computer tomography (CT) in patients with acute renal colic [76]. However, the radiation dose received during an abdominal CT cannot be justified in asymptomatic patients with pHPT, thus renal ultrasound (USS) is the screening investigation of choice. Ultrasound identifies calculi and nephrocalcinosis with a sensitivity of 64% and specificity of 100% [77, 78]. Renal function is assessed by measuring serum urea and creatinine combined with the calculation of the patients glomerular filtration rate.

Bone mineral density assessment using dual-energy X-ray absorptiometry (DEXA) is useful in assessing the presence and degree of osteoporosis in patients with pHPT. Criteria for osteopenia and osteoporosis based on DEXA scan results have been published by the World Health Organization (WHO) and are widely accepted [79]. DEXA calculates the bone mineral content divided by the area or volume

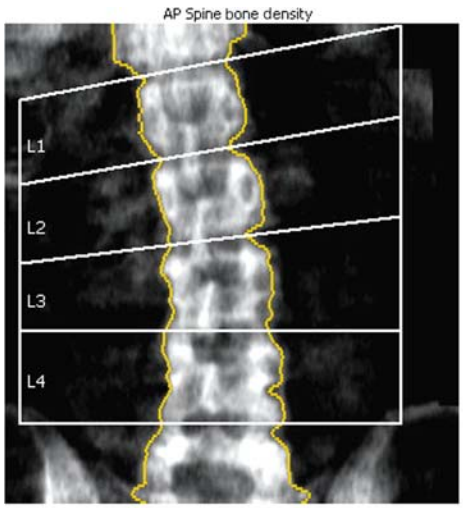
Table 16.5. Differential diagnosis of hypercalcemia

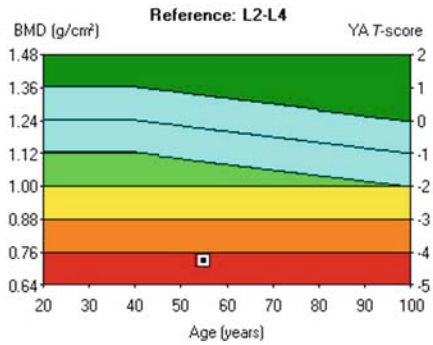
Category	Condition	Mechanism	Indication for Diagnosis
Malignancy	**Solid tumor (PTHrP)**: lung, kidney, squamous cell carcinomas of the head and neck/esophagus/ female genital tract	Osteolytic factors: PTHrP	Staging for malignancy (CT, skeletal X-ray, bone scan)
	Osteoclastic metastasis: breast, prostate	IL-1	Elevated tumor markers
	Hematological: multiple myeloma, lymphoma, leukemia	IL-6	Elevated PTHrP and calcitriol
	Hypercalcemic cytokines: interleukin 1 and 6, tumor necrosis factor alpha, prostaglandins	TNF	Low PTH
		Prostaglandins	
		Calcitriol	
Excess PTH	**Primary hyperparathyroidism**	Increased intestinal and renal Ca absorption	Raised PTH and Ca
	Sporadic or familial (MEN I and 2A)		
	Tertiary hyperparathyroidism	Osteolysis	
Increased bone turnover	Hyperthyroidism	Ca release from skeleton	Low PTH
	Immobilization		History
	Paget's disease		(X-rays, thyroid function, HIV serology)
	Acute intermittent porphyria		
	AIDS/HIV		
Excess vitamin D (Calcitriol induced)	**Granulomatous disease** (e.g., Sarcoidosis, tuberculosis, histoplasmosis)	Increased 1,25-dihydroxylated vitamin D	X-ray of lungs
			Serology and microbiology
			Raised calcitriol
Renal failure	**Secondary hyperparathyroidism**	Decrease in calciuria	Impaired renal function
	Milk alkali syndrome		History
	Aluminium intoxication		
Iatrogenic	Lithium	Increased PTH	Medication history
	Vitamin A intoxication (analogs used to treat acne)	Increased bone turnover	
	Thiazide diuretics		
	Vitamin D intoxication	Excess vitamin D	
	Tamoxifen		
	Theophylline		
	Salicylic acid intoxication		
Familial	**Familial hypocalciuric hypercalcemia**	CaSR defect causing decrease in calciuria	Hypocalciuria
			PTH normal or high
			Ca/creatinine clearance <0.01
	Idiopathic hypercalcemia of infancy	?PTHrP	Age and exclusion of other causes
			Low PTH
			Raised PTHrP
Miscellaneous	Addisonian crisis or glucocorticoid deficiency	Lack of PTH antagonist	Glucocorticoid tests
			Low PTH

of bone assessed in the region of interest and gives a value for BMD in that region. BMD measurements correlate with load-bearing capacity of the hip and spine and with the risk of fracture [80]. The measurements are expressed as a *T*-score and a *Z*-score which represent the patient's bone density in standard deviations from their respective controls [81].

The *T*-score is a measurement of bone density compared with that of 30-year-old Caucasian adult of the same gender with peak bone mass and is expressed in standard deviations

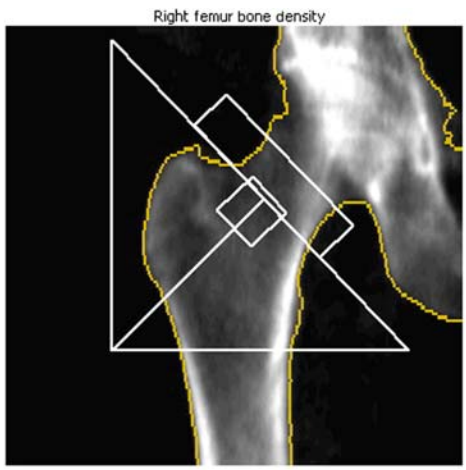
from the control value of 0. A score within one standard deviation (+1 to −1) is considered normal, between −1 and −2.5 is classified as osteopenia and a score below −2.5 is classified as osteoporosis. The *T*-score is used to estimate the risk of developing a fracture. Established osteoporosis is defined as a *T*-score below −2.5 and a history of at least one osteoporotic fracture (Figs. 16.3 and 16.4). The *Z*-score is a calculation of bone density compared with patients

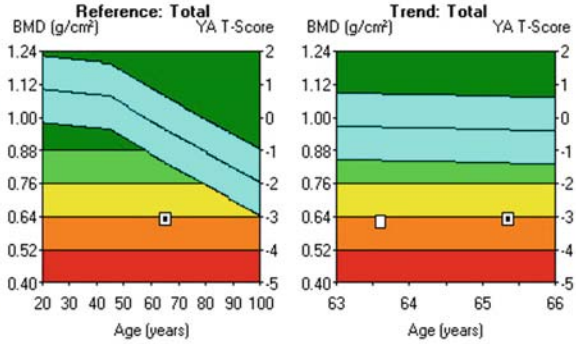




Region	BMD (g/cm²) [1]	Young-adult (%) [2]	Young-adult T-score [2]	Age-matched (%) [3]	Age-matched Z-score [3]
L1	0.670	58	-4.1	59	-3.9
L2	0.738	60	-4.2	61	-4.0
L3	0.726	59	-4.3	60	-4.1
L4	0.725	58	-4.3	60	-4.1
L2–L4	0.729	59	-4.3	60	-4.0

Fig. 16.3. DEXA scan of spine with severe osteoporosis.





Region	BMD (g/cm²) [1]	Young-adult (%) [2]	Young-adult T-score [2]	Age-matched (%) [3]	Age-matched Z-score [3]
Neck	0.656	67	-2.7	73	-2.0
Wards	0.424	47	-3.7	57	-2.4
Troch	0.523	66	-2.4	65	-2.5
Shaft	0.695	-	-	-	-
Total	0.628	63	-3.1	66	-2.7

Trend: Total

Measured Date	Age (years)	BMD (g/cm²) [1]	Change vs. Previous (g/cm²)	Change vs. Previous (%)
03/05/2007	65.3	0.628	0.007	1.1
04/08/2005	63.6	0.621	-	-

Fig. 16.4. DEXA scan of right femur with osteoporosis.

of the same age group, size, and gender and is therefore usually more relevant to clinical decision making in patients with pHPT.

Bone mineral density can be followed over time as a response to treatment or for surveillance as well as being a research end point. Newer tools aimed at measuring bone strength, in particular quantitative ultrasound, are also being studied. Indeed, quantitative ultrasound of the heel appears to be almost as predictive of hip fracture and all nonvertebral fractures as DEXA at the femoral neck [81].

Conclusions

Primary hyperparathyroidism is not as uncommon as thought in the past. It is now diagnosed more frequently and at an earlier stage in its natural history. Whilst asymptomatic disease may still be present, most patients present with a subtle 21st century version of the disease that is, however, far from innocuous. The diagnosis requires a thorough understanding of calcium metabolism and accurate biochemical investigations. Only once the diagnosis of pHPT has been unequivocally made, can definitive treatment with surgery be considered.

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17

Parathyroid Localization and Imaging

Jean-François Henry, David Taïeb and Sam Van Slycke

Introduction

For many years bilateral cervical exploration with identification of four glands remained the gold standard in parathyroid surgery, and routine preoperative imaging for initial surgery was considered unnecessary and not cost effective. In 1986, John L. Doppman stated "In my opinion, the only localizing study indicated in a patient with untreated primary hyperparathyroidism (HPT) is to localize an experienced parathyroid surgeon" [1]. Times have changed, and undoubtedly it is the progress of imaging studies that has modified the surgical management of patients with HPT and helped the development of new surgical techniques.

Many imaging modalities have been reported. In the past, when only invasive localization procedures [angiography and selective venous sampling (SVS)] were available, localization of abnormal parathyroid glands was limited to reoperative cases. Today, the development and the reported efficacy of noninvasive techniques have tempted many endocrinologists and many surgeons to order some of these new noninvasive techniques on patients undergoing first-time parathyroidectomy.

Moreover, more than half the surgeons performing parathyroid surgery now consider that bilateral parathyroid exploration is no longer the only option in all patients with HPT. Patients presenting with solitary adenoma can be candidates for new focused surgical procedures. This emphasizes the current role of preoperative localization studies in the surgical management of patient with primary HPT.

After an overview of the various noninvasive tests and invasive tests currently used we will discuss the indications for each of them.

Preoperative Localization Tests

Noninvasive Tests

Ultrasonography

High-resolution ultrasonography (US) with a probe of 7.5 or 10 MHz is used in first-line parathyroid imaging for many reasons. It is easily and quickly performed, and well tolerated by the patient. It does not require administration of contrast medium and does not emit radiation. It provides good anatomic information about masses in the neck and, when performed by expert radiologists, 95% of adenomas that weigh in excess of 1,000 mg can be identified. In addition it is the least expensive preoperative localization technique. However US can only assess the cervical region.

The sensitivity of US is operator and material dependent. The patient should be examined in the supine position with the neck in hyperextension. A pillow can be placed under the shoulders if the patient has a short neck. A high-frequency

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linear transducer (7.5–10 MHz) is used to obtain optimal depth penetration of 3–4 cm. A bilateral and comparative scan should be performed in transverse section, then in longitudinal section. In transverse section, the examination concentrates on an area defined by the longus colli muscles posteriorly, the thyroid gland anteriorly, the trachea medially, and the carotid artery laterally. The scan is then performed in cranial and caudal directions. An additional scan can be performed with the head of the patient turned away to the side, and during deglutition to optimize the latero-esophageal images. The anterosuperior mediastinum is examined by inclining the transducer deeply in a retrosternal direction.

Enlarged parathyroid glands appear as a homogeneous well-demarcated mass, which is hypoechoic in contrast to the hyperechoic thyroid tissue. They are usually solid, but large adenomas may have a cystic component.

The examiner should note the precise location with respect to surrounding structures, particularly the thyroid gland, and the depth from the skin. Enlarged superior parathyroid glands are usually found adjacent to the posterior aspect of the thyroid lobe (Fig. 17.1). They tend to migrate posteriorly and in a downward direction (Fig. 17.2), sometimes into the postero-superior mediastinum. Enlarged inferior parathyroid glands are usually found immediately adjacent to the inferior pole of the thyroid lobes (Fig. 17.3). In 25% of cases, they are found at a variable distance from the lower pole of a thyroid lobe (Fig. 17.4). These adenomas, lying in the thyrothymic ligament or in the upper cervical portion of the thymus, remain located

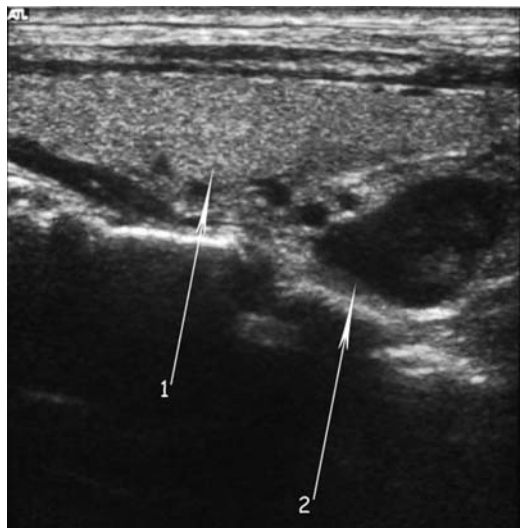

Fig. 17.2. Ultrasonography. *Arrow* 1: right thyroid lobe. *Arrow* 2: superior or inferior parathyroid adenoma posterior to the inferior pole of the thyroid lobe.

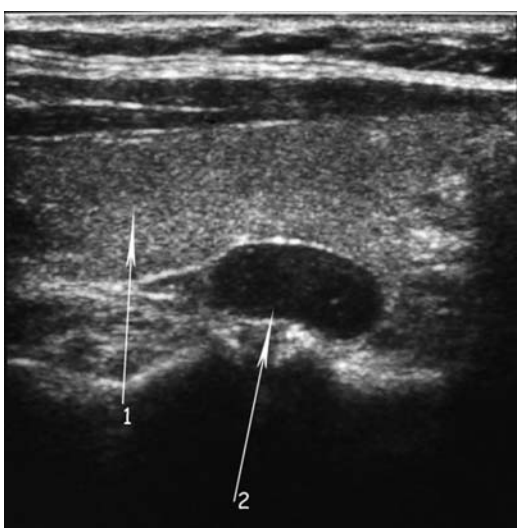

Fig. 17.1. Ultrasonography. *Arrow* 1: right thyroid lobe. *Arrow* 2: right superior parathyroid adenoma posterior to the two superior thirds of the thyroid lobe.

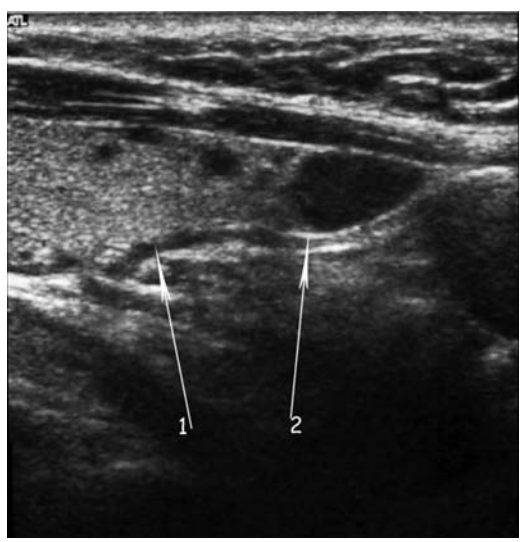

Fig. 17.3. Ultrasonography. *Arrow* 1: right thyroid lobe. *Arrow* 2: right inferior parathyroid adenoma located just below the tip of the inferior pole of thyroid lobe and in the superficial plane.

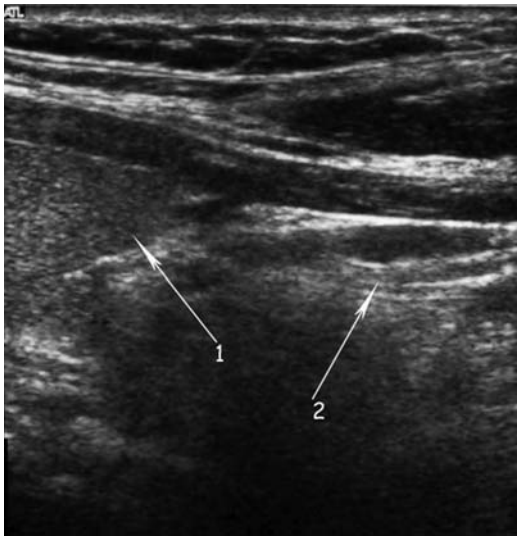

Fig. 17.4. Ultrasonography. *Arrow* 1: inferior pole of right thyroid lobe. *Arrow* 2: right inferior parathyroid adenoma along thyrothymic ligament.

superficially in the neck or in the superior mediastinum. Some inferior adenomas located at the posterolateral part of the inferior pole of the thyroid lobe tend to migrate posteriorly (Fig. 17.2) and in a downward direction, and are found in a paratracheal or a paraesophageal position. US provides good anatomic detail that permits the surgeon to know the exact location of the adenoma in the neck and make a judicious choice of surgical access.

Finally, a color-flow Doppler or a power-flow Doppler is performed to test the vascularization of the area and define the artery branches involved.

In patients without prior parathyroid surgery, US has been shown to have sensitivity and a specificity of 70–85% and 90–95%, respectively [2–5]. The sensitivity is highly dependent on the size of the parathyroid gland. The limit of detection is approximately 5 mm. Fewer than 50% of adenomas weighing less than 200 mg are identified by US. This can explain the reduced accuracy of US in the presence of parathyroid hyperplasia, in which enlargement of individual glands may be minimal [6, 7]. Other common causes of false-negative examinations include associated multinodular goiter, adenomas located in the tracheoesophageal groove which can be obscured by the acoustic shadow of the trachea, or the acoustic shadow of bone when located behind the clavicle or sternum. Sensitivity falls to 40% for reoperative localization since such patients have an increased incidence of ectopic mediastinal parathyroid adenomas or multiglandular disease (MGD) [8].

Intrathyroid parathyroid adenomas are well imaged by US but they have an ultrasonographic appearance indistinguishable from that of hypoechoic thyroid nodules. As for other nonparathyroid anatomical structures, the diagnosis can be confirmed by US-directed fine needle aspiration (FNA) for parathyroid hormone (PTH) which is highly sensitive and specific [9–11]. False-positive results vary from 15 to 20% [12, 13].

Many factors may explain the variable reported accuracy of US, but it is likely that preoperative US localization is highly dependent on the skill and experience of the examiner. US is particularly useful when used in conjunction with other modalities such as FNA and parathyroid scintigraphy.

Parathyroid Scintigraphy

Over recent decades, several protocols of parathyroid scintigraphy have been evaluated [14–16]. ^{201}Tl has been abandoned in parathyroid imaging since the introduction of ^{99m}Tc-sestamibi because of the poorer quality images and unfavorable dosimetry.

Coakley and coworkers first reported on the use of ^{99m}Tc-sestamibi for parathyroid

imaging [17]. Sestamibi (methoxy-isobutyl-isonitrile), a lipophilic compound, is radiolabeled with ^{99m}Tc-pertechnetate, using commercial lyophilized kits. Following injection, the radiopharmaceutical is rapidly and passively accumulated within the mitochondria of metabolically active cells, including thyroid and parathyroid cells. Tracer retention is dependent on several factors such as mitochondria content, cell cycle, and expression of P-glycoprotein efflux protein. Two protocols for sestamibi scanning are in current use: the single isotope-dual phase protocol and the subtraction protocol.

Taillefer and coworkers introduced the concept of single radiopharmaceutical/dual phase imaging [18]. This approach is based on the differential sestamibi retention between parathyroid and thyroid tissue. After injection of ^{99m}Tc-sestamibi, tracer retention is prolonged

in parathyroid hyperfunctioning lesions whereas it washes out more rapidly from normal thyroid tissue. This retention is presumably related to oxyphil cells in parathyroid lesions which are rich in mitochondria. The dual protocol requires early (15 min postinjection) and delayed images (at 1 and 2–3 h, depending on thyroid washout). Image acquisition is centered over the 140 Kev photopeak. On the early images, activity of the parathyroid lesion may be more intense, intense as, or less intense than thyroid activity. The detectability of disease is dependent on parathyroid–thyroid activity ratio and location of the tumour. On the delayed images, parathyroid lesions are easily identified (Fig. 17.5). However, washout of parathyroid lesions compared to thyroid may vary between subjects.

This technique is easy and simple, but has some specific limits such as parathyroid adenomas that clear sestamibi, low mitochondrial content (hyperplastic glands), and abnormal tracer retention in thyroid nodules (hyperfunctioning nodules, cancer). In cases of multinodular thyroid disease, additional further delayed images are sometimes needed to overcome these pitfalls.

When a subtraction protocol is used, ^{99m}Tc-sestamibi is used in conjunction with another radionuclide specific to the thyroid. ^{99m}Tc-pertechnetate and ^{123}I are the most widely used radioisotopes for thyroid scintigraphy. ^{99m}Tc-pertechnetate is obtained from $^{99Mo/99m}$Tc generators, has a half-life of 6 h and emits a 140-Kev gamma ray. ^{123}I is cyclotron produced, has a half-life of 13 h, and a gamma ray emission of 159 Kev. Both tracers are concentrated in thyrocytes via NIS protein but only ^{123}I is organified in thyroid follicles.

The main advantage of using ^{123}I is that thyroid and parathyroid images can be acquired simultaneously in a dual energy window set up. The disadvantage is the increased cost of the protocol related to ^{123}I. ^{123}I is usually injected 2–4 h before acquisition. With ^{99m}Tc-pertechnetate, the thyroid image can be acquired either before or after the completion of sestamibi acquisition. When ^{99m}Tc-pertechnetate is injected after sestamibi acquisition, both the dual phase protocol and the subtraction protocol can be performed. After normalization, thyroid images are digitally subtracted from sestamibi images. The residual image corresponds to an image of

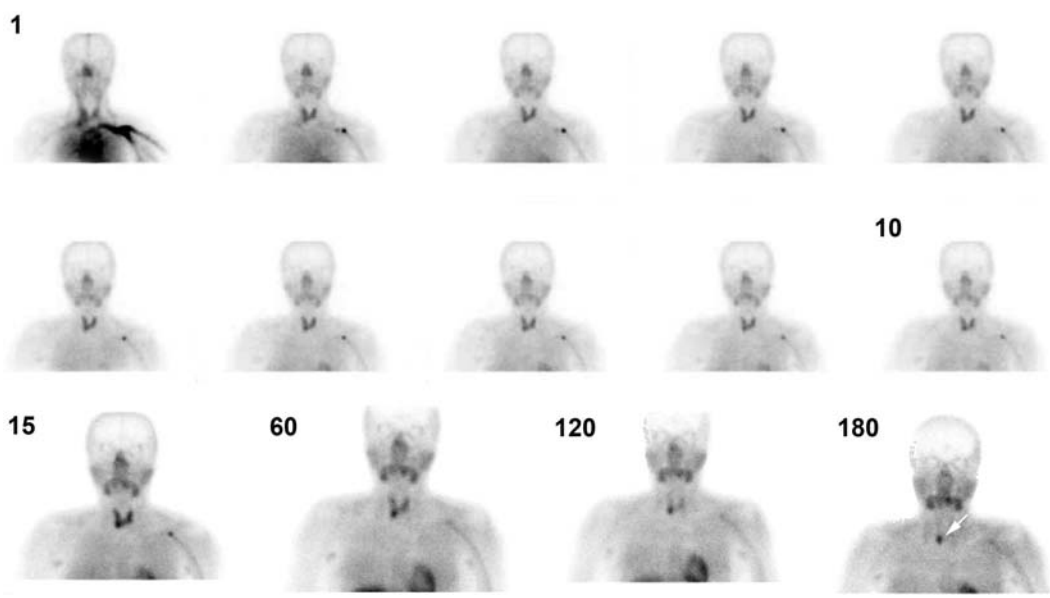

Fig. 17.5. Dual phase protocol: injection of 740 of ^{99m}Tc-sestamibi at T0. Dynamic planar images (from 1 to 10 min postinjection), static images at 15, 60, 120, and 180 min. The images shows more delayed washout of ^{99m}Tc-sestamibi from the parathyroid lesion (*white arrow*) than from the normal thyroid, resulting in increase contrast. A parallel hole collimator was used.

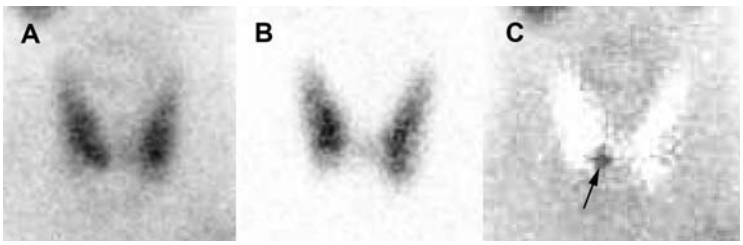

Fig. 17.6. Subtraction protocol: injection of 12 MBq of ^{123}I at T–2h, injection of 740 of ^{99m}Tc-sestamibi at T0, dual tracer planar pinhole acquisition at T + 3 (20 min acquisition). A typical example of parathyroid adenoma. (**A**) ^{99m}Tc-sestamibi pinhole planar image. (**B**) The ^{123}I scan shows a normal thyroid gland. (**C**) The subtraction image (^{99m}Tc-sestamibi-^{123}I) demonstrates a parathyroid lesion in the right lower pole of the thyroid. Simple visual comparison of two images is unable to reveal differences in tracer distribution. The detection of the adenoma needs digital subtraction of images (after normalization of thyroid image).

the parathyroid. Simple visual comparison of two images can also reveal differences in tracer distribution, but the detection of small lesions needs the computer manipulation of images (Fig. 17.6). When using two separate acquisitions for both isotopes, patient movement between data acquisitions may lead to false-positive images. Another potential pitfall of the subtraction protocol is reduced or absent ^{123}I or ^{99m}Tc-pertechnetate thyroid uptake, which renders the subtraction image invalid.

Parathyroid scintigraphy should include views of the neck and the mediastinum (from the angle of the mandible to the heart) because ectopic glands are widely distributed along the parathyroid cell migration routes.

The type of collimator used can affect the sensitivity of the procedure. The parallel hole collimator enables simultaneous imaging of both neck and mediastinum. The pinhole collimator provides higher resolution images and magnifies the structure being imaged. However, the field of view is smaller than for the parallel hole collimator, and images of the neck and mediastinum should be obtained separately.

Single-Photon Emission Tomography

Single-photon emission tomography (SPECT) or anterior oblique views can be helpful for more precise localization of adenomas. SPECT provides simultaneous 3D information on both the neck and the mediastinum. There is a further improvement in sensitivity and image quality when iterative reconstruction is used instead of filtered back-projection [19]. SPECT is particularly useful for reclassifying apparently inferior adenomas to superior adenomas prolapsed behind the lower pole of the thyroid gland. These adenomas can be located very deeply in the neck, in paraesophageal or retroesophageal locations, that may be missed by inexperienced surgeons (Figs. 17.7 and 17.8). By contrast, inferior glands are mostly located at the tip of the inferior pole of the thyroid lobe or along the thyrothymic tract on planar images and remain anterior on SPECT imaging (Fig. 17.9). SPECT also enables a better localization of large adenomas prolapsed in the mediastinum and ectopic glands (Figs. 17.10 and 17.11). There is no consensus regarding the timing of SPECT acquisition. Our preference is to perform SPECT 45–60 min after ^{99m}Tc-sestamibi injection because there is sufficient residual activity in thyroid for determining the relative position of parathyroid adenomas. Finally, the use of SPECT–CT fusion images is particularly helpful for localizing ectopic glands (Fig. 17.12).

There is no consensus regarding which imaging protocol should be used. The subtraction method seems to have a higher sensitivity than dual phase imaging [20–24]. However, only a few studies have compared both procedures in an intrapatient analysis. The reported sensitivity of parathyroid scintigraphy ranges from 70 to 100%, and mainly depends upon gland weight and PTH values, but is not related to calcium levels. SPECT may provide improvement in sensitivity in comparison to planar imaging [25–29]. In our experience, sensitivity reaches 90% when PTH >150 ng/ml or gland weight >1,000 mg, with only marginal improvement in sensitivity with SPECT [30]. In smaller lesions, sensitivity may vary between tumors.

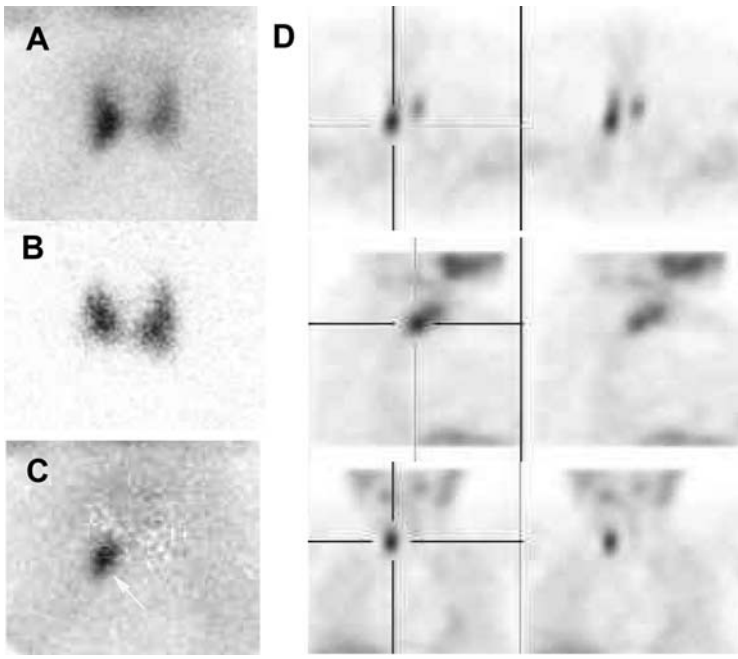

Fig. 17.7. Protocol: injection of 12 MBq of ^{123}I at T-2 h, injection of 740 of ^{99m}Tc-sestaMIBI at T0, dual tracer planar pinhole acquisition at T + 3 (20 min acquisition), SPECT at T + 45 min (30 s/projection). For SPECT, image was acquired with a 20% window centered over the 140-keV photopeak. Planar pinhole (**A**: ^{99m}Tc-sestamibi, **B**: ^{123}I, **C**: subtraction images) and SPECT images (**D**) of parathyroid adenomas. The posterior extension of the adenoma on SPECT images is highly suggestive of P4 origin, despite its apparent right inferior origin on planar images (*white arrow*).

Discrepancies between studies could be related to several factors including differences in imaging protocols (including radiopharmaceuticals used, tracer activities, collimators used, delays for image acquisitions, and interpretation criteria) and patient selection (goiter, gland weights, and PTH values).

As parathyroid scintigraphy is often used to direct focused surgical approaches, the results should be evaluated in relation to the surgeon's choice of operative procedure (adapted versus nonadapted to the parathyroid disease). A study showing only a single parathyroid lesion in a patient with double hyperfunctioning adenomas should be interpreted as a false-positive result because it should lead to a nonadapted focused surgical approach with a subsequent surgical conversion. By contrast, a negative study in the presence of MGD results in adapted bilateral open-surgery and should be interpreted as true-negative study for parathyroid adenoma.

Using these modified criteria, the positive predictive value of scintigraphy for identifying uniglandular disease is greater than 95% [25, 31, 32].

The most common cause of false-positive results is the solid benign thyroid nodule, either solitary or as part of a multiglandular gland. Therefore the specificity of parathyroid scintigraphy is highly dependent upon the patient population. Subtraction images, late ^{99m}Tc-sestamibi delayed acquisitions (2–3 h), and SPECT should improve specificity. Other potential false-positive findings are related to thyroid carcinomas, thymomas, and metastatic or inflammatory lymph nodes.

False-negative results are attributed to small parathyroid lesions, cystic adenomas (after necrosis or cystic degeneration), and hyperplastic glands in cases of sporadic or familial MGDs. The incidence of MGD is about 20% when parathyroid scintigraphy is negative compared with 1–2% when scintigraphy is positive for a single adenoma [32]. The reduced sensitivity for detecting MGD is not clearly understood and does not seem to be entirely related to lower

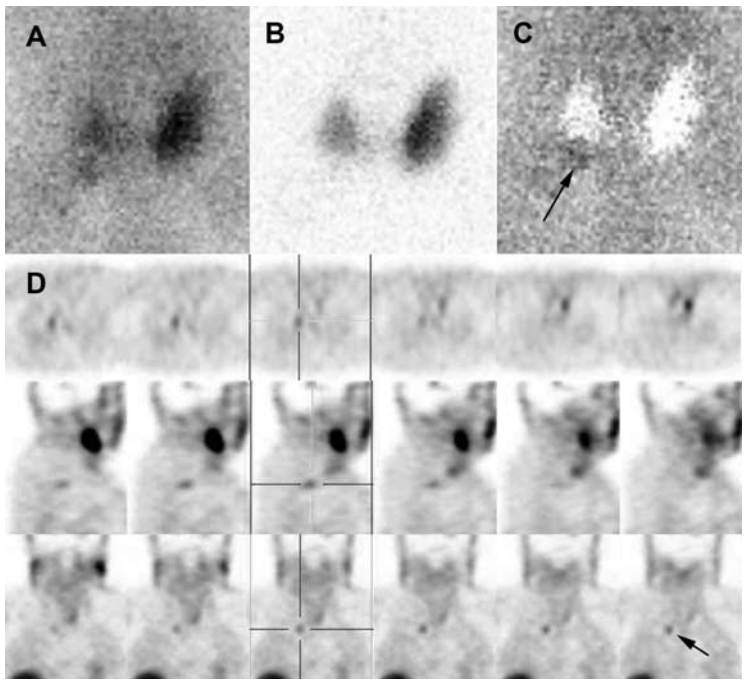

Fig. 17.8. Parathyroid scintigraphy revealed a typical right P4 adenoma. (**A**) ^{99m}Tc-sestamibi, (**B**) ^{123}I, (**C**) subtraction, (**D**) SPECT images (axial, sagittal, and coronal imaging planes). Planar pinhole subtraction images reveal a focal moderate accumulation of ^{99m}Tc-sestamibi located under the left thyroid lobe (**C**). SPECT images demonstrate that the gland is prolapsed behind the thyroid gland and is extended posteriorly (*black arrows*).

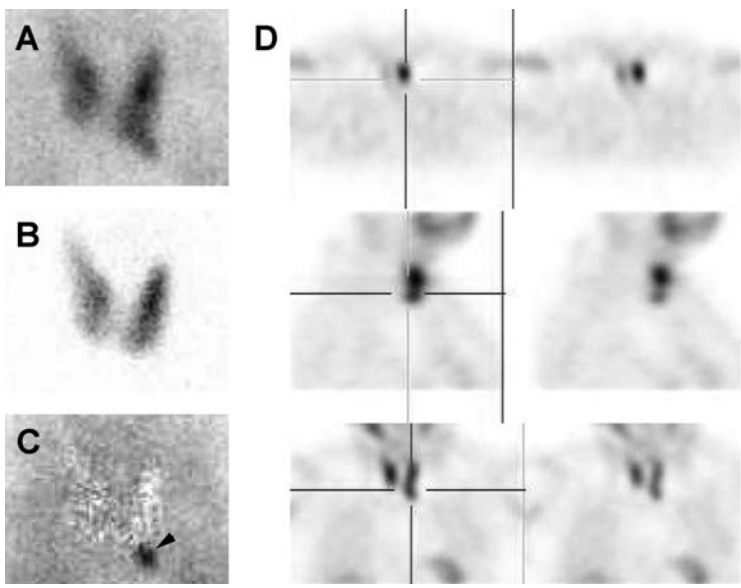

Fig. 17.9. Planar pinhole (**A**: ^{99m}Tc-sestamibi, **B**: ^{123}I, **C**: subtraction images) and SPECT images (**D**) of parathyroid adenomas. Typical P3 adenoma which is located at the tip of the left inferior lobe on planar images and remains anterior on SPECT images.

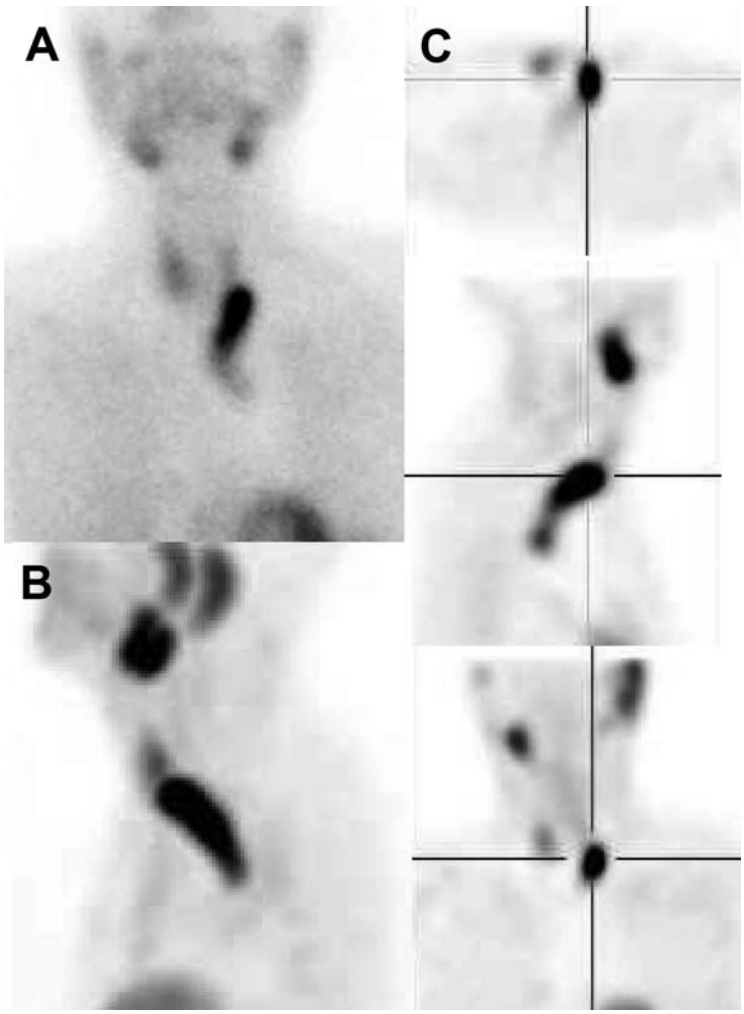

Fig. 17.10. The ^{99m}Tc-sestamibi scintigraphy shows a left large parathyroid adenoma extending into the mediastinum. (**A**) Planar anterior image at 45 min postinjection. (**B**) 3D image of SPECT acquisition. (**C**) Orthogonal views (axial, sagittal, and coronal) of SPECT.

gland weights. Negative results have been attributed to overexpression of sestamibi efflux proteins, fewer mitochondrial-rich oxyphil cells or low active growth phase.

As in other imaging techniques true-negative results correspond to misdiagnoses including laboratory errors, secondary hyperparathormonemia related to vitamin D deficiency, false hypercalcemia (hypergammaglobulinemia), non-PTH 1-84 dependant hypercalcemia (paraneoplastic PTHrp secretion, bone metastases, sarcoidosis, hyperthyroidism, drugs), and familial hypocalciuric hypercalcemia. Normal parathyroid glands are not visible on parathyroid scintigraphy.

Only a few studies have demonstrated the role of SPECT acquisitions for improving the localization of adenomas in patients operated through focused surgical approaches [30, 33].

Computed Tomography

Computed tomography (CT) is a useful technique for parathyroid localization because of its ability to detect ectopic glands in anterior, middle, and

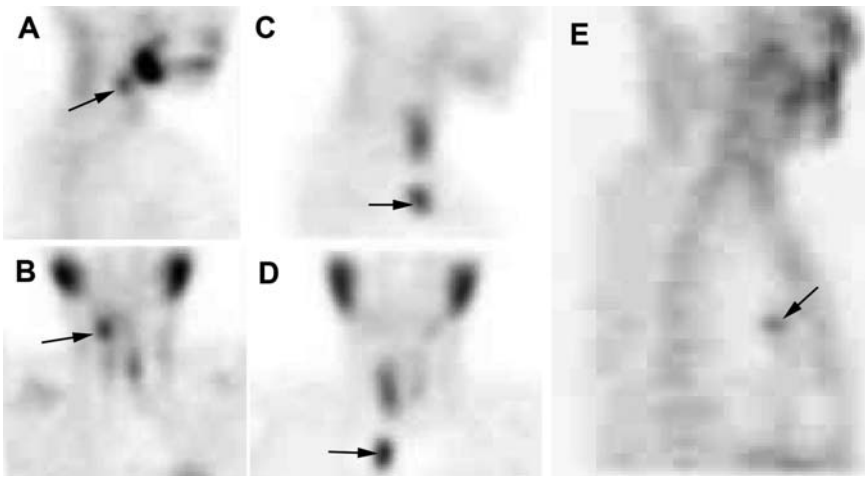

Fig. 17.11. Examples of ectopic parathyroid adenomas. (**A** and **B**) P4-derived adenoma. (**C** and **D**) Intrathymic right P3-derived adenoma. (**E**) P3-derived adenoma located in the aorto-pulmonary window (sagittal plane).

posterosuperior mediastinum. Most of these glands are inaccessible for ultrasound. CT should be done with thin cuts (3–5 mm). Nevertheless, the limitations of CT remain related to the size of the adenoma. Intravenous contrast material should be used to obtain the best results because many parathyroid adenomas will enhance. CT is less effective in the neck than in the mediastinum. It is useful for deep-seated retroesophageal glands in the neck but less effective for parathyroid glands close to the thyroid. Sparkler effects observed from surgical clips used in prior

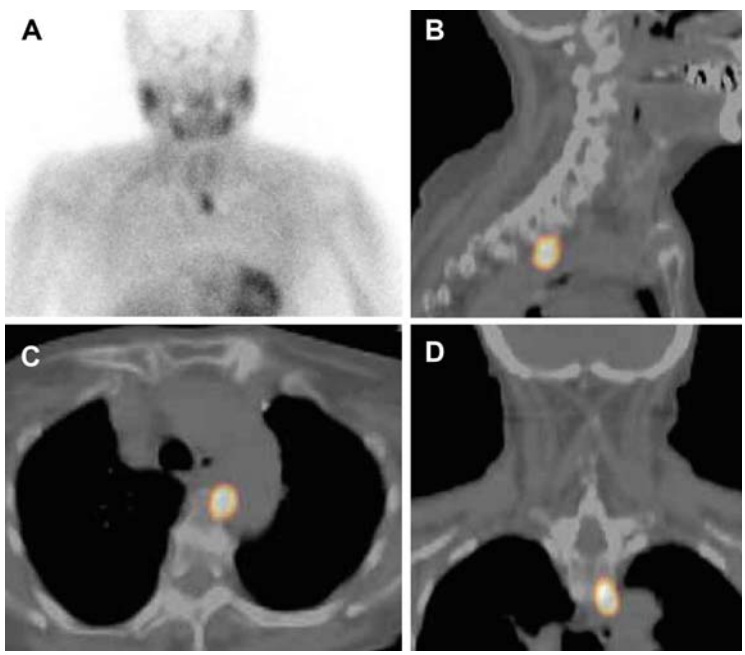

Fig. 17.12. ^{99m}Tc-sestamibi scintigraphy. (**A**) Planar images find a left inferior parathyroid adenoma. (**B**–**D**) SPECT images (sagittal, axial, and coronal imaging planes) help in the diagnosis of paraesophageal ectopic adenoma.

operations, scanning artefacts resulting from breathing and swallowing can make interpretation of images more difficult. Lymph nodes and tortuous vessels can also be mistaken for enlarged parathyroid glands. False-positive results are more frequent than with other modalities and rates may reach 50% [34]. The sensitivity reported ranges from 16 to 70% [8, 12, 13, 35–44].

The use of 4-dimensional CT (4D-CT) for parathyroid imaging has recently been reported [45]. 4D-CT gives exquisitely detailed multiplanar images and allows the visualization of differences in the perfusion characteristics of hyperfunctioning parathyroid glands compared with normal glands and other structures. This technique provides both anatomic and functional information in a single study, and seems very promising.

CT imaging of the parathyroid glands is relatively expensive, exposes the patient to radiation, and requires the administration of contrast medium. Nevertheless, CT is particularly useful for identifying mediastinal adenomas missed at initial surgery. However the high rate of false-positive results means it must be used in conjunction with a sestamibi scan. Once the precise location in the mediastinum of the missing gland is determined, the surgeon can choose the best surgical approach.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) provides excellent anatomic detail and is slightly more sensitive than CT. It does not require intravenous contrast and is not subject to the "sparkler effect" or shoulder artifact. Nevertheless, MRI is expensive and patient compliance is sometimes limited by claustrophobia.

Parathyroid adenomas typically have a low signal intensity in T1-weighted imaging, and a high signal intensity in T2-weighted imaging [42]. They may enhance with gadolinium.

Sensitivity ranges from 50 to 88% [8, 13, 35–38, 41, 43, 46–50]. Like CT, MRI is particularly useful for identifying ectopic parathyroid adenomas. Sensitivity approaches 90% for adenomas in the mediastinum. False-positive results are due to enlarged lymph nodes and thyroid abnormalities. MRI has significant drawbacks; size of detection is limited to adenomas >5 mm, and localization of the superior glands is problematic since they lie posterior to the thyroid.

MRI is usually reserved as a second line test for localization in reoperative parathyroid surgery when US and sestamibi scan have failed to identify an abnormal parathyroid gland which is probably located in the mediastinum.

Positron Emission Tomography

Positron emission tomography (PET) imaging has been reported in limited studies. Three radiopharmaceutics have been evaluated: ^{18}F-fluorodeoxyglucose (^{18}F-FDG), ^{11}C-methionine, and ^{18}F-fluorodihydroxyphenylalanine (^{18}F-FDOPA) [51, 52]. Methionine PET scanning was found to have a high sensitivity (about 85–90%); however, 11C-methionine has the practical disadvantage that the half-life of ^{11}C is very short (20 min) and requires an on-site cyclotron. ^{18}F-FDG is less sensitive. ^{18}F-FDOPA is unable to detect parathyroid adenomas and should not be used [53]. CT-PET co-registration is useful for localizing ectopic adenomas.

Currently, PET cannot be recommended for routine use and should be reserved for patients with persistent or recurrent HPT, when other tests have been unhelpful. In addition, PET is not available in all centers and the cost is high compared with other investigations.

Invasive Tests

Selective Venous Sampling

SVS for PTH measurement requires an experienced and skilled interventional radiologist. It is a very sensitive test which depends on gland function rather than size. Establishing an angiographic roadmap is recommended before performing SVS. Venous catheterization is performed through a femoral vein with sampling from large veins such as the jugular vein, innominate vein, superior cava. Smaller veins, such as superior, middle, and inferior thyroid veins are sampled when present, as are the thymic and vertebral veins. The samples must be taken as selectively as possible from the smallest venous branches to provide a precise gradient map as a guide for the surgeon [54]. A gradient of at least twofold in the PTH level is required for a result to be significant [49, 55–58].

In the published reports, sensitivity and specificity of the SVS range from 63 to 94.7% and 86 to 100%, respectively [59].

SVS cannot be routinely proposed because of the associated risks of morbidity; venous thrombosis, hematoma, prolonged radiation exposure, and contrast load. In addition, it is an expensive technique. It should be reserved for reoperative parathyroid surgery when other investigations have failed.

Selective Angiography

Proper parathyroid angiography includes examination of the thyrocervical trunks for glands in lower cervical sites, the carotid arteries and superior thyroid arteries for upper cervical sites, and internal mammary arteries for thymic and mediastinal sites. Parathyroid adenomas appear highly vascularized with an ovoid or round blush. Adenoma size limit is 4 mm. Sensitivity approaches 60% [8, 60, 61]. False positives are due to thyroid nodules and enlarged lymph nodes. In selected cases, it is possible to perform angiographic embolization of the adenoma [62]. This technique is only indicated for poor-risk surgical patients with persistent HPT related to a mediastinal parathyroid adenoma.

As in SVS, parathyroid angiography is a difficult and expensive technique with potentially serious complications. For these reasons it should be reserved for reoperative localization when other tests have failed.

Fine Needle Aspiration

FNA performed under sonographic or CT guidance may help distinguish a parathyroid tumor from other structures. It is a minimally invasive test used in reoperative cases to confirm the diagnosis of parathyroid tissue. PTH determination is more helpful than cytological examination because the sample may be insufficient and because differentiating between parathyroid and thyroid tissue can be difficult. FNA with PTH determination is highly sensitive and specific [10, 63]. The use of FNA is limited in small adenomas. FNA can be combined with alcohol ablation but persistent or recurrent HPT is likely and the procedure has to be repeated [64]. In addition inferior laryngeal nerve injury has been reported. This nonoperative procedure requires an expert radiologist and should be reserved for patients refusing surgery.

Intraoperative Tests

The Parathyroid Surgeon

Although today many modalities of parathyroid localization are available, one should keep in mind that the success of a parathyroid operation is above all based on the experience of the surgeon, a thorough knowledge of the anatomy, and on an understanding of the embryological evolution of the glands. The failure rate of an initial cervical exploration performed by an experienced parathyroid surgeon does not exceed 5%. Ideally, the failure rate should not exceed the incidence of ectopic glands deeply located in the mediastinum and inaccessible from a cervical approach. Without preoperative localization, the experienced parathyroid surgeon is still one of the most sensitive, specific, and cost effective "tools" to identify an abnormal parathyroid gland.

Methylene Blue Staining

An intravenous infusion of saline mixed with methylene blue is given after anesthesia induction: abnormal parathyroid glands stain a dark to light blue whereas normal glands remain unstained. This method speeds identification of the glands in initial operation, and has been reported to be safe, effective, and inexpensive but is today used by few surgeons [65].

Intraoperative US

Intraoperative US using a 10-mHz transducer may be useful in reoperative cases. The procedure is performed with either a dedicated sterile intraoperative transducer or one draped in a sterile sheath. It requires a learning curve. This method has been particularly recommended for the identification of adenomas hidden in dense scar tissue and for intrathyroidal parathyroid

adenomas. Operating time can be reduced significantly [66].

Radio-Guided Parathyroid Surgery

This test is characterized by the use of an intraoperative probe to direct the dissection according to the level of radioactivity [67]. The operation must be carried out within 3.5 h of the radiopharmaceutical injection. There is a "window" of optimal timing between injection of the pharmaceutical agent (^{99m}Tc sestamibi) and using the probe in the operating room. The optimal situation occurs when the thyroid has washed out its nuclear tag and the parathyroid remains radioactive. Typically, a window between 1.5 and 2.5 h is ideal for the vast majority of patients. Resected adenomas emit radioactivity of greater than 20% of the post excision background activity. This confirms the diagnosis of hyperfunctional parathyroid tissue and reduces the number of diagnostic frozen sections. Fat, lymph nodes, and thyroid nodules do not show this level of radioactivity. When exploring the superior mediastinum it must be remembered that false-positive readings can be due to radioactivity emitted by the heart.

Radio-guided parathyroid surgery can be used in both initial surgery and reoperative cases. It has the potential to reduce operative time [68]. It does not require the use QPTH measurements [67]. Excellent results have been reported [69].However, controversy exists, and some authors consider that radio-guided parathyroidectomy does not add a significant advantage, and is heavy and time sensitive to apply [70].

Intraoperative SVS for QPTH Measurement

The intraoperative QPTH assay enables the surgeon to perform SVS by direct punction into both internal jugular veins and innominate vein. This technique can help the surgeon, during the procedure, to localize or lateralize a hypersecreting gland in the neck or in the superior mediastinum.

Indications for Localization Tests

One should emphasize that parathyroid imaging is not a technique that should be used to make or to confirm the diagnosis of HPT; this is achieved by metabolic testing. This is a fundamental point particularly when a parathyroid tumor is incidentally discovered during US examination indicated for thyroid disease.

Are parathyroid localization studies useful? The answer is yes, but they must be selected according to availability, experience, success rate, cost, benefit, and risk for the patient. The least invasive and the least costly studies should be used first. Today one can consider that:

1 There is a debate regarding the routine use of localization studies for initial standard cervicotomy in patients with primary HPT.
2 The role of imaging studies prior to initial surgery in patients with secondary/tertiary HPT also remains controversial.
3 Preoperative localization is mandatory for focused parathyroid approaches.
4 Preoperative imaging is undeniably valuable for patients who have persistent or recurrent HPT.

Initial Bilateral Cervical Exploration

In the past, routine preoperative imaging for initial bilateral parathyroid exploration was considered unnecessary and not cost effective (Dopmann) [1]. Indeed, when performed by an experienced endocrine surgeon, the success rate of this procedure was reported to be 95–98% [71]. The failure rate, in most cases related to ectopic glands, not in the neck but located deeply in the mediastinum and virtually inaccessible from the cervical route, was considered too low to justify systematic preoperative imaging. Nevertheless, not all parathyroid operations are performed by expert parathyroid surgeons, and there has been improvement in noninvasive localizing techniques. This explains that an increasing number of authors currently advocate the use of preoperative localization of abnormal parathyroid glands before all parathyroidectomies.

Moreover, because most surgeons accept that bilateral cervical exploration is not the

only indicated procedure in a patient with a solitary parathyroid adenoma, parathyroid surgeons are today highly dependent upon the result of preoperative imaging to make a judicious choice between a bilateral cervical exploration and a focused approach. Once contraindications have been eliminated, all patients with sporadic primary HPT who are considered potential candidates for a Focused parathyroidectomy must undergo localization studies. These procedures will only be indicated for patients in whom a single adenoma has beenclearly localized. In most centers this is an argument for the routine use of US and sestamibi scan in all patients with untreated primary HPT.

Numerous benefits of the successful localization of abnormal parathyroid glands have been reported. Proper localization directs and limits surgical exploration and therefore may reduce surgical failure rate, complication rates, and operative time [72–74].

Only an inexpensive, highly sensitive and highly specific and noninvasive test should be considered for initial standard cervicotomy. This test does not exist but many authors routinely use US and/or sestamibi scan. According to the availability and experience in different centers these localization studies can help the surgeon by localizing the abnormal gland. Other tests are not indicated even when both US and sestamibi scan are negative. It remains questionable whether the routine use of US or sestamibi scan is justified and financially sustainable in all cases of primary HPT [75].

Secondary/Tertiary HPT

Whether preoperative localization studies are helpful to achieve complete parathyroid identification in renal HPT remains controversial. Many authors consider that localization prior to initial surgery does not have a significant role in planning the surgical intervention and is unnecessary as these patients systematically undergo a bilateral cervical exploration, to identify all four glands and to search for a supernumerary gland in the neck or superior mediastinum.

The aim of imaging when used in secondary/tertiary HPT is to limit the surgical exploration, reduce the operative time, and above all to detect supernumerary and ectopic glands that are present in up to 25% of patients. Prior to initial surgery, only noninvasive imaging tests should be considered, i.e., US/sestamibi scans as first line, and CT or MRI when there is suspicion of an ectopic mediastinal location. Patients with secondary HPT tend to have large glands and the sensitivity and specificity of these imaging modalities are higher than for primary hyperplasia. A sensitivity of 45–70% for US and of 30–65% for sestamibi scanning has been reported [76–78]. However, it is very rare that all four glands are imaged in the same patient.

Minimally Invasive Parathyroidectomy

The concept of new minimally invasive techniques is based on the fact that 85% of patients will have single-gland disease. The common thread of new minimally invasive techniques is that the approach is targeted on one specific parathyroid gland. In most cases the exploration of other glands is not performed. Therefore, the success of limited techniques largely depends on accurate preoperative localization.

Because surgery is targeted on one specific gland, patients suspected of having multigland disease are not suitable for these limited procedures. Today the surgeon is therefore highly dependent upon the quality of preoperative localization to make a judicious choice for either a focused or a conventional approach.

Most institutions use US or sestamibi scan, either alone or most commonly in combination. These imaging studies complement each other. Sestamibi scan allows identification of hyperfunctioning glands but provides few anatomic details. In contrast, US provides little information about function but is much more informative about anatomic detail. If the US and the nuclear scan do not correlate with a solitary lesion at the same site, a traditional 4-gland open procedure is preferable. However, if the lesion is solitary and confirmed by both studies, a focused procedure can be proposed. It has been demonstrated that the risk of MGD is nearly zero when both studies are positive and concordant. In this case the use of QPTH is questionable. The risk of MGD has been found to be 3.6% when only one imaging method is positive [32]. When available, 4D-CT, providing both anatomic and functional information can be used instead of both US and sestamibi scan [45].

Preoperative imaging may also have a role for the choice between different focused approaches described [79]. Depending on a posterior or anterior location of the adenoma in the neck, the surgeon can choose a central or a lateral approach. The lateral approach, which allows direct access to the lateral and posterior aspects of the thyroid lobe, is particularly suitable for patients with adenoma located posteriorly in the neck. In contrast, the central access is more convenient for patients with inferior parathyroid adenomas located superficially in the neck or in the superior mediastinum.

Finally, preoperative imaging may also have a role for the choice between a mini-open procedure or a video-assisted or endoscopic procedure [80]. The need for an endoscope during minimaly invasive parathyroidectomy (MIP) may be determined by the location of the parathyroid adenoma. In our opinion, the use of the endoscope must be recommended when the parathyroid adenoma becomes intimate with the recurrent laryngeal nerve, that is, when the adenoma is located in the retro-thyroidal area. The endoscope offers not only a magnified view of anatomical details but also a perfect lighting of the area of dissection. The quality of the surgical image provided by the endoscope is undoubtedly superior to the one obtained with frontal lamps and magnifying loupes. We consider that mini-open approaches using a skin incision of no more than 2 cm should be used only when the nerve is not at risk during the dissection, which is when the adenoma is superficially located in the neck. Therefore the need to know preoperatively when the nerve is at risk reinforces the role of imaging studies for localizing deep-seated adenomas.

Persistent or Recurrent HPT

The diagnosis of persistent or recurrent PHPT must be reconfirmed biochemically and must be unequivocal. Once again, the surgeon should keep in mind that the diagnosis of PHPT is not established by parathyroid imaging, and that false-positive results of imaging techniques do exist. Once the diagnosis has been reconfirmed, the potential benefit of reoperation must be weighed against the operative risk in the individual patient. For example, mild asymptomatic hypercalcemia, which was considered an indication for primary surgery, may not necessarily justify the risks of reoperation.

It has been demonstrated that when the first operation is performed by an inexperienced surgeon, reoperation by a more expert surgeon is successful in 95% of cases without any preoperative tumoral localization [81–83]. Nevertheless, today preoperative imaging is undeniably valuable for any patient who has persistent or recurrent HPT and particularly for patients who have been operated on by expert surgeons. Apart from improving the prospects of success, preoperative localization of the tumor reduces the operating time and the operative morbidity. Today, most parathyroid surgeons consider that surgery for persistent or recurrent HPT should be performed only after positive localization studies.

Many modalities of noninvasive and invasive imaging can be applied preoperatively to localize the parathyroid glands. These modalities should be selected according to availability, cost, and experience. The topographic diagnosis should ideally be established by concordant results of two different investigations, one providing good anatomic information and the other providing functional information.

Therefore, most authors consider that US and sestamibi scan should be performed routinely as the first-line work up for persistent or recurrent HPT. When these two tests suggest a unique enlarged and hyperfunctional gland in the neck further additional localization is not required. 4D-CT, when available, is an alternative to US/sestamibi [45].When a sestamibi scan suggests an ectopic mediastinal location, CT or MRI are mandatory to confirm the localization and to give additional anatomic information. CT scan and MRI are also indicated for patients in whom both US and sestamibi scan have failed to localize a lesion. The appropriate approach to the mediastinum is dependent upon the precise localization. Most mediastinal adenomas located in the posterior or anterior mediastinum above the aortic arch can be excised through the neck [13, 35, 36, 40, 44, 84, 85]. Only adenomas located deep in the anterior or middle mediastinum require a thoracic approach. Precise localization can allow approaches less invasive than a sternal split or thoracotomy. Mini-anterior mediastinotomy or left thoracoscopy may be preferable to a partial or a total sternotomy [86, 87].

When sestamibi or US scans are equivocal, image-guided FNA may help distinguish a

parathyroid tumor from other structures in the neck. For a suspected mediastinal localization, when sestamibi, CT, or MRI are equivocal, PET-FDG may be useful.

Invasive procedures including SVS for PTH or selective angiography, should be performed only if noninvasive procedures are inconclusive.

After total parathyroidectomy and autotransplantation in patients with renal HPT, recurrences can occur not only on the grafts but also secondary to a supernumerary gland in the neck or the mediastinum. When there is no evidence that the recurrence is graft-dependant, the Casanova test can be used to evaluate whether the origin of the recurrence is a residual gland or grafted tissue [88].

Finally, whether reoperative surgery is indicated when localization studies are negative remains questionable. The surgeon must keep in mind that localization failures may be due to an incorrect diagnosis. With the advent of a reliable radioimmunoassay for intact PTH, other causes of hypercalcemia can be easily eliminated. Particular thought should be given to the syndrome of benign familial hypocalciuric hypercalcemia (BFHH). It has also been reported that 1 month after surgery for primary HPT, elevated serum PTH levels are observed in up to 30% of patients despite normalization of calcium levels. In some cases elevated PTH levels are an adaptative reaction to renal dysfunction or vitamin D deficiency. It has also been demonstrated that these patients can show decreased peripheral sensitivity to PTH [89].

If the diagnosis of HPT remains unequivocal the persistent or recurrent disease is more likely due to parathyroid hyperplasia than solitary adenoma. In our experience, negative preoperative localization studies are highly predictive of MGD [32]. The sporadic or familial nature of the HPT should be determined. Study of the operative and histology reports from previous operations may be useful to determine if there is a possibility of an MGD or, of an undiscovered solitary adenoma. If biopsy has not been performed, the reported identification of a parathyroid gland is questionable. The number of glands identified, their gross appearance, and possible excision should be carefully noted. Their embryonic origin, e.g., third or fourth branchial pouch, should be determined. An understanding of the embryonic development and the embryonic migration of the parathyroid glands is of paramount importance in these circumstances. In our opinion, in the absence of localization, only cervical reoperation may be indicated. Mediastinal explorations using a thoracic access are too invasive and too hazardous to be recommended. When there is a strong suspicion of MGD the suggested operation is a revision of the transverse cervicotomy. The entire parathyroid system must be explored. This also involves a search for supernumerary glands and a bilateral thymectomy if not previously excised. When a nonlocalized parathyroid adenoma is suspected, the procedure may be more selective and guided by the results of previous operations. When available, intraoperative ultrasound and gamma-probe may be helpful here. QPTH monitoring and cryopreservation are also recommended in these patients. Other possible causes of persistent or recurrent disease, without confirmatory localization studies, are parathyroid carcinoma and parathyromatosis. Patients, previously operated on for parathyroid carcinoma, may have multiple undetectable metastatic lesions. In the case of parathyromatosis, multiple small nodules of hyperfunctioning parathyroid tissue, locally scattered in the neck, may be also not visualized by localization studies. In both scenarios medical therapy should be considered.

Conclusion

Refinements in parathyroid localization studies have led to a reassessment of their role in the management of patient with HPT. Twenty years ago the role of parathyroid localization was as a preoperative localization procedure. Because bilateral neck exploration was the only surgical option and because this procedure was successful in 95–98% of cases when performed by experienced endocrine surgeons, preoperative localization in patients with untreated HPT was rarely indicated and was reserved for patients with persistent or recurrent disease.

In recent years, there has been a progressive shift in the management of patients with HPT that has been driven by technological advances. Improvement in noninvasive localizing techniques is certainly the main factor that today enables the surgeon to perform focused

parathyroid surgery. Preoperative imaging has a role not only to inform the choice between traditional surgery and focused surgery but also the choice between different surgical access and between different minimally invasive techniques. In contrast to the surgeon performing traditional parathyroid surgery 20 years ago, today the parathyroid surgeon depends highly on the quality of preoperative imaging studies to make a judicious choice for the appropriate indications for, and application of, the currently available surgical techniques.

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18

Intraoperative PTH Monitoring

Denise Carneiro-Pla and George L. Irvin

Introduction

Sporadic primary hyperparathyroidism (SPHPT) is caused by the autonomous hypersecretion of one or more parathyroid glands. The only definitive treatment of this disease is surgical excision of all hyperfunctioning parathyroid tissue. In the past decade, intraoperative parathormone monitoring (IPM), used to guide the surgeon during parathyroidectomy, has changed the operative management of SPHPT.

IPM guided parathyroidectomy was first introduced in 1990 and has since grown in acceptance around the world. This technique involves the rapid measurement of plasma parathormone levels during parathyroidectomy. Changes in these hormone levels confirm the extent of operative excision necessary to remove all abnormal parathyroids while preserving in situ other normally functioning glands. Several rapid PTH determinations are done at the surgeon's request and timed to coordinate the changing hormone levels occurring with the operative events taking place during parathyroidectomy. The understanding and use of these intraoperative hormone dynamics has changed the operative approach from a routine bilateral neck exploration (BNE) with excision based on the surgeon's judgment of grossly enlarged glands, to a quantitative excision based on the hypersecretion of abnormal parathyroid tissue.

Intraoperative PTH monitoring is now being used in many medical centers and is emphasized in current training programs. Knowledge of this technique is expected by the board of general surgery. There have been more than 400 published articles and numerous presentations at national and international meetings on parathyroidectomy guided by intraoperative PTH monitoring over the past 16 years. Currently, the use of this surgical approach is considered a standard of care by many surgeons.

The purpose of this chapter is to describe in detail the protocol for intraoperative PTH monitoring and the usefulness of this adjunct during parathyroidectomy for SPHPT. Although less well defined, the use of IPM to treat hyperparathyroidism associated with other etiologies such as secondary, tertiary, isolated familial hyperparathyroidism (IFHPT), parathyroid cancer, and multiple endocrine neoplasia (MEN) syndrome will be also described.

History

Human parathormone has been measured since 1968 but its intraoperative use was not practical until 1988 when Nussbaum described a method, using a two-site antibody immunoradiometric assay (IRMA), which measured the intact molecule of parathormone (1-84) [1]. That same year, his group demonstrated that serum PTH levels decreased rapidly after excision of a

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hyperfunctioning parathyroid gland. Blood samples were collected during parathyroidectomy and measured by the IRMA after the procedure. These investigators suggested that an intraoperative parathyroid hormone assay could be used to prevent operative failures [1, 2]. In 1990, Flentje et al. modified the PTH assay by decreasing the laboratory turnaround time to one hour and attempted to use it perioperatively [3]. The same group described in detail the marked changes in PTH levels observed during parathyroidectomy. Although they measured the PTH after the completion of the operation, it was clearly shown that PTH dropped after excision of the abnormal parathyroid gland. That same year, Chapuis, using Nussbaum's assay, described 13 patients in whom he found that the PTH level decreased more than 70% from a baseline value in a 20-min sample taken after gland excision. In one patient, the PTH decrease was only 38%, but he stated that the preoperative PTH level was close to the upper limit of the normal range and his hypercalcemia was transient [4]

Later, a study was published describing the use of a rapid intraoperative PTH measurement using an IRMA [5]. Parathyroidectomy guided exclusively by IPM was described in 1991, and a BNE was found to be unnecessary since a marked decrease in the serum PTH level confirmed complete excision of all hyperfunctioning glands resulting in operative success [5]

In 1996, the technical advantages of immunochemiluminescence over the immunoradioisotopic methods for hormone measurement were pointed out, and the "quick" PTH assay became commercially available for intraoperative use. At the present time, there are at least four PTH assays with capabilities for intraoperative use having turnaround times ranging from 8 to 20 minutes. The cost of these parathyroid hormone assays for intraoperative use has decreased over time and along with several clinical benefits from its incorporation as a surgical adjunct, such as shorter operative time, ambulatory surgery, and a focused, limited exploration resulting in an improved operative success rate, this adjunct has become a cost-effective part of parathyroidectomy.

Which Patients Benefit from Intraoperative PTH Monitoring?

IPM has been extensively studied and proven to be very accurate in predicting operative success or failure in patients with SPHPT [6–14]. There are studies that evaluate the use of IPM in patients with MEN, parathyroid cancer, secondary, tertiary, and IFHPT, but the IPM accuracy in predicting outcome in these patients has not been fully established [14–23]

Sporadic Primary Hyperparathyroidism

IPM was first designed to prevent operative failure due to overlooked multiglandular disease (MGD) in patients with SPHPT. When used intraoperatively, this surgical adjunct has been shown to have an accuracy rate of 97–98% in predicting postoperative calcium levels. However, when evaluating the accuracy of IPM, it is paramount to point out that this methodology is directly dependent on the criteria and blood-sampling times used during the parathyroidectomy. The protocol for blood sampling will be described in detail in the next section.

The criterion used to predict postoperative success, which is defined as eucalcemia for 6 months or more following parathyroidectomy, is a drop in the peripheral PTH level of >50% from the highest either preincision or preexcision level 10 minutes after all hyperfunctioning tissue has been excised and is called the ">50% PTH drop" criterion in this chapter [24]. The long-term follow-up of patients with SPHPT with parathyroidectomy guided by IPM and fulfilling the criterion described above has shown an operative success rate of 97% and a late recurrence rate of 1.5% [8] These results are similar to the best operative outcomes of parathyroidectomy performed with BNE and excision guided by parathyroid gland size and histopathology. Furthermore, these excellent operative success rates have been achieved with a low incidence of multiple gland excision (3%) [8]

How does Intraoperative PTH Monitoring Guide Parathyroidectomy?

The technique for intraoperative PTH monitoring to guide parathyroidectomy is meticulous and the success of this surgical adjunct depends exclusively on the surgeons' knowledge of PTH dynamics and the protocol used during the operative procedure.

Protocol for Blood Sampling

In the operating room or in the holding area, a large bore catheter is placed in one of the upper extremities, preferably in the antecubital vein. The venous access should be tested for adequate flow after the upper extremities are positioned along the patient's body. Often the access will not be adequate after the patient is positioned and since sample timing is critical, it is important to assure that blood samples can be drawn promptly during the operation. If necessary, an arterial line can be used for this purpose. After a good access is secured, an intravenous extension is used to allow the anesthesiologist to draw blood using a 3-way stopcock at specific times to be determined by the surgeon. It is very important to discard 10cc of blood before the sample is collected for PTH measurement to avoid sample dilution caused by the saline in the IV tubing. Blood sample dilution can cause a false PTH reading, for example, if the 10-minute sample is diluted resulting in an incorrect lower PTH level, this could result in a false PTH percentage drop potentially causing an operative failure. On the other hand, if the two initial plasma samples are diluted, the 10-minute PTH level might not drop properly potentially leading to unnecessary further neck exploration. The blood samples should be placed in an EDTA tube and shaken to avoid coagulation.

The first sample is called "preincision" and should be taken before cervical incision is made or when intravenous access is obtained. All samples should be measured in the same conditions, with the same PTH kits and curve calibrations. Plasma samples measured in the initial work-up or by a previous standard laboratory assay cannot be used to calculate the intraoperative PTH changes.

The second sample to be drawn is called "preexcision," and it is collected just before the suspected abnormal gland's blood supply is clamped. This sample is very important especially in cases where manipulation of the abnormal parathyroid gland increases the PTH level significantly. A preexcision level collected too early in the dissection could potentially miss the peak of PTH level as a result of further manipulation of the abnormal parathyroid gland. This could potentially lead to a false-negative result, meaning the PTH level will not drop sufficiently ($<$50%) due to a missed peak of the hormone level. Therefore, it is important to take the sample just before the complete blood supply of the parathyroid gland is interrupted. Often this level has already dropped significantly from the preincision level, which signifies that the abnormal parathyroid gland blood supply was already disrupted and the PTH level has already decreased. This is the reason the preincision and preexcision samples should be obtained in every procedure in order to correctly calculate the $>$50% drop (Fig. 18.1A,B). The third sample is taken 5 minutes after the gland is excised. This sample is not crucial for the decision making, but some surgeons use this sample to proceed with the closure of the cervical incision in cases where the PTH has already dropped $>$50% from the highest of the two previous samples. This measurement helps to shorten the operative time with the 10-minute sample assuring the complete excision of all hypersecreting tissue.

The final sample is collected 10 minutes after gland excision. A sufficient decrease in this sample allows the surgeon to finish the procedure without further exploration or visualization of the remaining normally secreting glands. On the other hand, if the hormone level fails to drop, it signals that more hypersecreting tissue is likely present. The surgeon is thus directed to continue the exploration, with samples collected after each additional suspected tissue is excised until the PTH drops adequately. The same protocol above described with 5- and 10-minute sample measurements should be used for each suspicious tissue excised until all abnormal parathyroid glands are removed. We

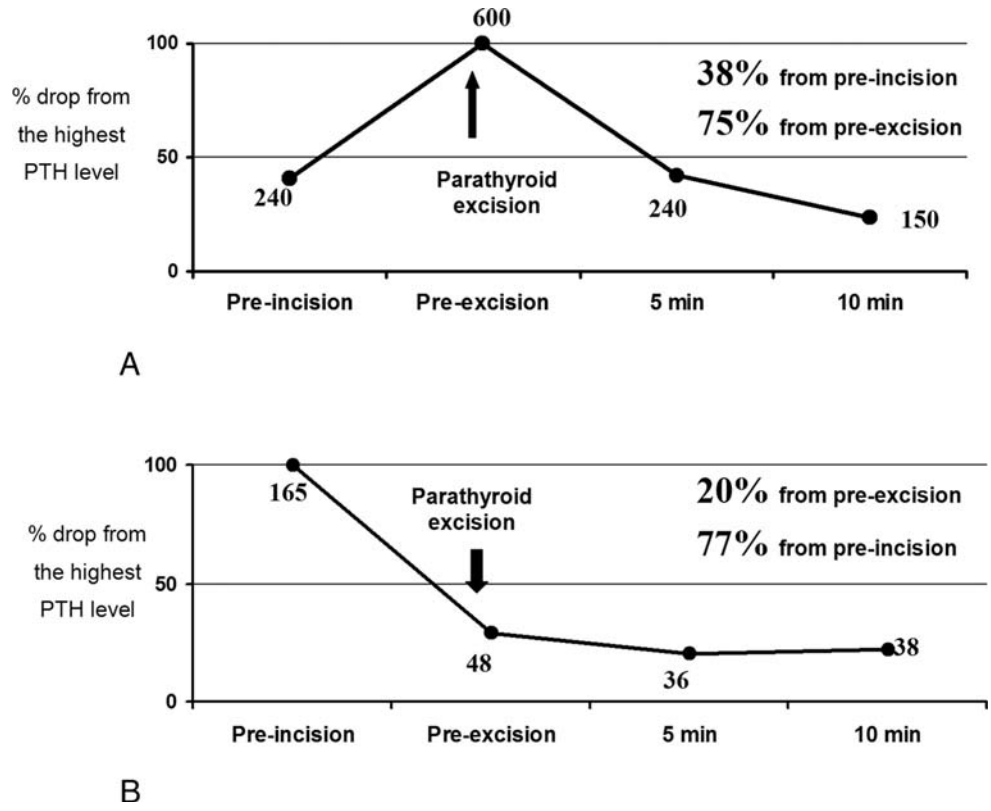

Fig. 18.1. Graphic showing the intraoperative PTH dynamics of two patients with successful parathyroidectomies following excision of a single hypersecreting parathyroid gland. This shows why preexcision (**A**) and preincision (**B**) samples are needed to calculate the drop in the PTH level 10 minutes after gland excision. (**A**) Insufficient PTH drop in 10 minutes from the preincision level (38%). (**B**) Insufficient PTH drop in 10 minutes from preexcision level (20%). A is adapted from Irvin GL, Carneiro-Pla DM, Solorzano CC. Intraoperative parathyroid hormone assay-guided parathyroidectomy. In: Fisher JE, Bland KI, eds., Mastery of surgery, 5th ed. Philadelphia: Lippincott, Williams & Wilkins, 2007.

may collect a sample at 20 minutes after a gland excision when the 10-minute level has only dropped between 40 and 49% from the highest value. If at 20 minutes the PTH drops sufficiently, the operation is completed. On the other hand, if at 10 minutes there is an insignificant PTH drop, continued exploration of the neck is done without collecting the 20-minute sample.

Some surgeons prefer to use different sites for blood collection other than peripheral vessels, which usually are the internal or external jugular veins, while others use various protocols with different blood sample timings such as 15, 20, or 30 minutes post excision [25–27]. There are protocols that use only one sample before the parathyroid gland is excised, either preincision or preexcision usually called "baseline level" [29–34]. The consequences of these variations will be described in the following section, but it is important to be aware that it can potentially affect the accuracy of IPM in predicting complete excision [24].

Calculation of IPM Accuracy Using the ">50% PTH Drop" Criterion

The accuracy of IPM using the ">50% PTH drop" criterion in predicting postoperative calcium levels was determined using these definitions (Table 18.1): True positive (TP) is defined

Table 18.1. Definitions used to calculate the accuracy of ">50% PTH drop" criterion in predicting postoperative calcium levels for at least 6 months

">50% PTH drop" criterion	Operative success (eucalcemia for ≥6 months)	Operative failure (high calcium + high PTH <6 months)
>50% PTH drop 1Ó	True positive	False positive
<50% PTH drop 1Ó	False negative	True negative

when the intraoperative PTH level drops >50% from the highest initial value 10 minutes after gland excision and the patient is eucalcemic for at least 6 months; true negative (TN) is defined when the PTH fails to drop >50% and another hyperfunctioning gland is found or the patient has persistent HPT (hypercalcemia and high PTH level within 6 months of the operation). False negative (FN) is present when the PTH does not drop sufficiently in 10 minutes and the patient is eucalcemic for at least 6 months without any additional parathyroid gland excision; false positive (FP) is when the PTH meets the criterion for cure but the patient is hypercalcemic postoperatively.

Which IPM Criteria Should be Used?

It is important to emphasize that all rapid intraoperative PTH assays only measure parathormone plasma level at a specific point in time. The variable that determines the accuracy of IPM is the criteria applied to the intraoperative PTH levels and the protocol used, not the intraoperative assay itself. It is important to clarify this fact since there are many studies that question the validity of IPM in guiding parathyroidectomy, when the only variable in question is the methodology and the intraoperative criteria used to predict a specific outcome [28–33].

The criteria described in this chapter, the ">50% PTH drop" criterion, which has been used with excellent results for the past 15 years, is a drop in the peripheral PTH level ≥50% from the highest value, in either the preincision or the preexcision sample, 10 minutes after all hyperfunctioning tissue is excised. This specific drop predicts postoperative calcium levels with an accuracy of 98% correctly assuring operative success [24].

The surgeon's decision of which IPM criteria should be used has recently become controversial leading to studies that described the accuracy of various IPM criteria in predicting operative success. To determine which criteria have the best accuracy in predicting postoperative calcium levels, we have described a careful comparison between the intraoperative criteria available in the literature and our 341 consecutive parathyroidectomies that were guided exclusively by the ">50% PTH drop" criterion which requires the least PTH drop to predict cure [24]. The other referenced criteria were more strict using in addition to the >50% PTH drop: (1) a return of PTH to the normal range at 10 minutes, (2) final PTH value below the preincision level, (3) drop of >50% from only the preincision, or (4) drop of >50% from only the preexcision level. The overall accuracy, positive and negative predictive value of these criteria, and the incidence of TP, TN, FP, and FN of each one of them are shown in Tables 18.2 and 18.3. These results were determined based on the postoperative outcome of patients with parathyroidectomy guided by the least strict criterion. All patients had 6 months or longer follow-up (average 33, range 6–105) and all operative failures were included in the study. The patient selection and their postoperative outcome confirmed the real incidence of MGD in this population. Patients who were eucalcemic for at least 6 months with only one gland excised were considered to have single gland disease and the ones who had more than one hyperperfunctioning parathyroid gland identified either by IPM or by operative failure after single gland excision were considered to have MGD. As shown in Table 18.3, using the ">50% PTH drop" criterion which was the least strict of all criteria studied, MGD was missed due to FP IPM results in three (0.9%) patients. Unnecessary further neck exploration could have been potentially done due to FN results in another

Table 18.2. IPM accuracy in predicting postoperative calcium levels with different criteria [24]

IPM criteria	Sensitivity (TP/TP + FN)	Specificity (TN/TN + FP)	Positive predictive value (TP/TP + FP)	Negative predictive value (TN/TN + FN)	Overall accuracy (TP + TN/TP + TN + FP + FN)
"$>$50% PTH drop" criterion:	97%	96%	99%	88%	97%
$\geq$50% from highest at 10′					
(1) $\geq$50% from preinc. at 10′	83%	99%	99%	56%	86%
(2) $\geq$50% from highest at 10′ + within NR	75%	98%	99%	42%	79%
(3) $\geq$50% from highest at 10′ + below preinc.	94%	97%	99%	77%	95%
(4) $\geq$50% from highest at 5′	88%	97%	99%	64%	90%
(5) $\geq$50% from preexc. at 10′	85%	97%	100%	58%	87%

TP, true positive; TN, true negative; FP, false positive; FN, false negative; preinc., preincision; NR, normal range; preexc., preexcision.
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2.6% of patients. This criterion had a low incidence of FP and the lowest incidence of FN results therefore presenting with the highest overall accuracy in predicting postoperative calcium levels [24].

Table 18.3. Incidence of false-positive and false-negative results when using different criteria compared to the "$>$50% PTH drop" criterion

IPM criteria	FP (%)	FN (%)
$>$50% PTH drop: $\geq$ 50% from highest at 10′	0.9	2.6
(1) $\geq$50% from pre-inc. at 10′	0.3	16*
(2) $\geq$50% from highest at 10′ + within NR	0.4	24*
(3) $\geq$50% from highest at 10′ + below pre-inc.	0.6	6*
(4) $\geq$50% from highest at 5′	0.6	11*
(5) $\geq$50% from pre-excision at 10′	0.6	15*

FP, false positive; FN, false negative
*Statistically significant p value <0.05; NR, normal range. Adapted from Surgery, vol. 134, Carneiro DM, Solorzano CC, Nader MC, Ramirez M, Irvin GL 3rd, Comparison of intraoperative iPTH assay (QPTH) criteria in guiding parathyroidectomy: which criterion is the most accurate?, 973–9; discussion 979–81, Copyright 2003, with permission from Elsevier.

Others have used a similar study design to analyze which criteria have the best accuracy [34–36]. These studies have suggested that IPM with the "$>$50% PTH drop" criterion was not accurate in predicting operative success because a more strict criteria was used intraoperatively to guided the surgeon to further exploration and another enlarged parathyroid was found and excised. These authors claimed that the "$>$50% PTH drop" criterion failed to show the presence of MGD in 43% of these patients which were identified as having more than one enlarged gland by the use of a more strict criteria (additional intraoperative drop to the normal range or below preincision). If the "$>$50% PTH drop" criterion fails to identify MGD as suggested by theses studies because an additional enlarged gland was found, a higher incidence of operative failure should be present when the "$>$50% PTH drop" criterion is used. The operative failure rate with the "$>$50% PTH drop" criterion is only 3% which was often predicted intraoperatively. These failures were usually not caused by missed MGD, but inability to find and excised the abnormal gland(s) [6–8, 24]. To support these operative results, other

published outcomes from various centers that use the same criterion do not show a higher incidence of operative failure due to missed multiglandular disease [9–14, 37, 38]. Therefore, the incidence of MGD when a more strict criteria is used should be questioned. Indirectly, we can conclude that those additional glands found and excised in patients subjected to more strict criteria were not autonomously hypersecreting since they were not excised in our patients, because the ">50% PTH drop" criterion was met, and these patients were successfully treated.

Since operative failure using the ">50% PTH drop" criterion is not higher, some predict that these enlarged glands left in situ would cause a higher incidence of early recurrent HPT. When the incidence of recurrent HPT was studied, this condition occurred in 1.5% of the patients followed over an average of 3 years which is similar to the published recurrent disease incidence in patients that underwent BNE (1.5–5%) [8].

Clark et al., in an important study, described the results of a randomized trial in which patients were treated with BNE with resection of all enlarged glands or limited parathyroidectomy guided by IPM. The patients from the IPM group, in whom parathyroidectomy was guided by parathyroid function had a lower incidence of MGD (15% less), suggesting that maybe the additional enlarged glands removed during BNE were not hyperfunctioning [38]. The published operative outcome of patients with parathyroidectomy guided by IPM and the ">50% PTH drop" criterion shows that these additional "enlarged" glands were not hyperfunctioning at the time of surgery, and so far they are not autonomously hypersecreting causing hypercalcemia now averaging 4 years after parathyroidectomy.

Additional Uses and Advantages of the Intraoperative PTH Assay

Differential Internal Jugular Venous Sampling

This technique, which is positive in 70–76% of cases, can guide the surgeon to the side of the neck harboring the hypersecreting parathyroid gland when the preoperative localization studies are negative or equivocal [39–41]. Samples from the internal jugular and peripheral veins are taken before skin incision for rapid PTH measurement. Figure 18.2 demonstrates a positive differential jugular venous test in a patient with a right-sided hypersecreting parathyroid

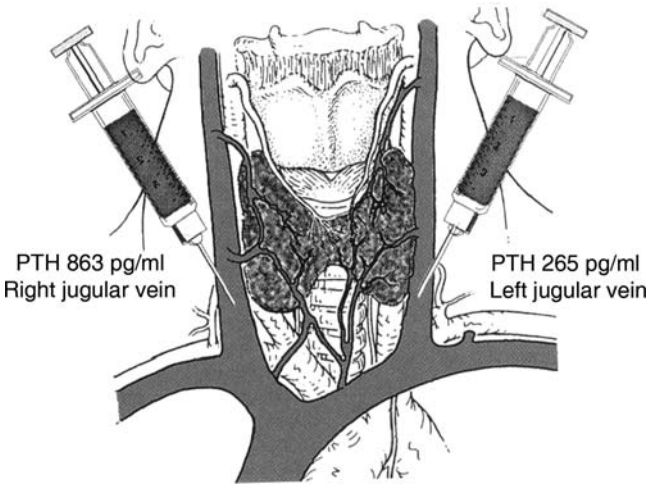

Fig. 18.2. Positive jugular venous sampling performed in the operating room guiding the surgeon the side of the neck harboring the hypersecreting parathyroid gland in patient with negative MIBI scan allowing successful unilateral neck exploration. Reprinted with modification from Operative Techniques in General Surgery, vol. 1, Irvin GL III, Carneiro DM. Rapid parathyroid hormone assay-guided exploration, pp. 18–27, Copyright 1999, with permission from Elsevier.

gland and a negative sestamibi scan allowing a successful unilateral neck exploration when single gland involvement was confirmed by IPM.

Biochemical Fine-Needle Aspiration

This technique was first described by Perrier et al. and consists of measuring PTH levels in tissue samples obtained from fine-needle aspirations. The PTH levels in the cells differentiate parathyroid from other tissues, such as thyroid nodules or lymph nodes, with a specificity of 100% [42]. A 25-gauge needle attached to a syringe is used to collect the tissue sample. The content that is aspirated, is diluted with 1cc of saline solution, centrifuged, and the supernatant is used for PTH measurement intraoperatively by a rapid assay. This technique provides rapid tissue identification without frozen section, and it can be helpful when gland identification is difficult, for example, in the case of an intrathyroidal parathyroid gland, an indeterminate exophytic thyroid nodule, or enlarged lymph nodes. Such tissue identification may decrease the operative time by preventing further dissection of suspicious, but nonparathyroid, tissue.

Decreases in Operative Time and Costs

After excision of the hypersecreting gland(s) has been assured by meeting the IPM criterion, the surgeon may complete the cervical exploration without examination and/or biopsy of the remaining parathyroid glands. This decreases the operative time because continued search for normally functioning glands is unnecessary. With biochemical confirmation predicting a return to eucalcemia, frozen section histopathology is not necessary, thereby decreasing the operative time. Most of the cost savings is in the ability to perform ambulatory surgery without an overnight stay [44–47].

Improves Operative Success

IPM and the "$>$50% PTH drop" criterion have improved the success rate of initial and reoperative parathyroidectomies in patients with SPHPT [6, 47]. In patients having initial parathyroidectomies, operative success improved from 94% with the previous standard approach with BNE and excision of all enlarged glands based on the surgeon's judgment of size to 97% with limited parathyroidectomy guided by parathyroid hypersecretion. Furthermore, the operative success rate increased from 76% with BNE to 94% with IPM guided excision in reoperative patients [6].

Recognizes Abnormal Glands More Accurately than Histopathology

It has been shown that IPM is more accurate in recognizing the function of the remaining glands left in situ than histopathology. The assumption is that patients with diagnosis of adenoma have single gland disease while hyperplasia was associated with multiple gland involvement. A study showed that 64% of successfully treated patients with SPHPT and single gland involvement identified by IPM were postoperatively diagnosed as having hyperplasia [48]. Histology would be incorrect in guiding the extent of the resection in most cases, therefore should not be used to guide parathyroidectomy.

Limitations of Intraoperative PTH Monitoring

IPM and "$>$50% PTH Drop" Criterion Does not Predict the Size of the Remaining Normally Secreting Parathyroid Glands

Some surgeons using IPM during BNEs have published the finding of a second enlarged gland after successful excision of a single hypersecreting parathyroid confirmed by an intraoperative drop in hormone levels. Because these enlarged, normally functioning glands were interpreted as "second adenomas" and were excised, the IPM results were reported as false positive because eucalcemia was achieved [28–33]. The criterion used in our studies does not predict the size of the remaining normally functioning glands. In our patients, these glands were not hypersecreting either at the time of the operation, confirmed by the return to eucalcemia, or found to be responsible for

recurrent hypercalcemia during the postoperative period, which now averages 4 years. This emphasizes that abnormal secretion is not necessarily associated with parathyroid gland size [49, 50]. This can also be supported by the fact that when parathyroid excision is guided by hormone secretion, 9–19% fewer glands are removed with a 97% success rate, when compared with gland resection guided by surgeon's judgment of size [51]. Therefore, we can indirectly conclude that those enlarged glands left in situ were not hyperfunctioning.

IPM Does Not Predict PTH Levels in Postoperative Eucalcemic Patients

Some authors have pointed out that the use of IPM with the ">50% PTH drop" criterion in parathyroidectomy fails to predict high PTH levels in postoperative eucalcemic patients [26]. It is known that despite the operative approach used, PTH levels are often elevated in eucalcemic patients following successful parathyroidectomy. Many of these patients will have their PTH levels returned to normal several months after parathyroidectomy [51–55]. Carty et al. and Bergenfelz et al. have suggested that these high PTH levels are compensatory, with parathyroid glands only responding to a deficit in total body calcium [52, 55]. In addition, most of the patients who were replaced with calcium and Vitamin D had a return of PTH to normal range over time and the recurrence rate remained very low.

IPM Does Not Assure Hypersecretion of the First Gland Excised in MGD

IPM cannot determine the function of the first excised parathyroid gland if the PTH level does not drop sufficiently and an additional gland is found and excised. IPM does not differentiate the first gland from an enlarged normally functioning parathyroid since the hormone level remained high after its removal.

IPM Does Not Predict Late Recurrence

There is no difference in the operative hormone dynamics between patients who are biochemically cured and those who developed recurrent hyperparathyroidism [8].

IPM Does Not Guarantee Operative Success

IPM predicts, but does not always prevent, operative failure in patients whose offending gland(s) could not be found by BNE performed by an experienced surgeon or operative failure due to misdiagnosis. In most operative failures, IPM correctly predicts postoperative hypercalcemia with a specificity of 96% [24].

The Cost of Intraoperative PTH Assays

Some of the intraoperative PTH assays are expensive, but the costs of this adjunct have decreased significantly over the past years. The benefits of IPM, however, compensate for its cost by allowing a shorter operative time, no need for frozen section histopathology and eliminating an overnight hospital stay in most patients [43–46].

Isolated Familial Hyperparathyroidism or Non-MEN Familial Hyperparathyroidism

The use of IPM to guide resection in patients with isolated familial HPT has been previously described [22]. In the past, patients with IFHPT (first-degree family members with primary HPT and no other endocrinopathies) were treated based on the principle applied to patients with MEN with BNE and 3½ gland or total parathyroidectomy with autotransplantation. Operative success with these extensive excisions was achieved in most patients but recurrent disease occurred in 19–23%, and permanent hypoparathyroidism was found in 13–41%. The report of successful parathryoidectomy with single gland excision triggered the use of IPM in the surgical treatment of patients with IFHPT [22]. When IPM with the ">50% PTH drop" criterion was used to guide the excision in these patients, operative

Table 18.4. Accuracy of various intraoperative PTH criteria in predicting operative success in patients with secondary hyperparathyroidism

Studies	Number of Patients	Criteria	Prediction of cure (%)	Overall accuracy
Ikeda [16]	18	PTH drop <45 pg/ml at 30′[a]	94% cured[b]	NR
Weber [15]	95	(1) PTH drop > 90% 10′	(1) 97% cured[c]	NR
		(2) PTH drop to NR in 10′	(2) 100% cured[c]	NR
Seehofer [21]	153	(1) PTH drop <150 at 15′	(1) 99% cured [b]	(1) 74%
		(2) PTH drop >70% from T0 at 15′	(2) 94% cured [b]	(2) 92%
		(3) Either <150 or >70% drop at 15′	(3) 99% cured [b]	(3) 94%

[a]Intraoperative PTH assay used the whole intact PTH or Bio intact PTH.
[b]Cure defined as normal PTH levels for 6 months.
[c]Cure defined as normal calcium and normal PTH.

outcome was correctly predicted with a sensitivity and specificity of 100 and 80%, respectively. The success rate of this operative approach in patients with IFHPT was 93% with a recurrence rate of 9% over an average follow-up of 2 years. Multiglandular disease was present in 13% when excision was guided by parathyroid hypersecretion alone as opposed to the previously published incidence of 45–75% when excision was guided by parathyroid gland size and histopathology. False-positive results and operative failure in these patients was 7%.

Although the accuracy of IPM in guiding parathyroidectomy in patients with IFHPT is lower than in patients with SPHPT, we offer this approach as long as they understand and accept that in exchange for a limited neck dissection and a decreased incidence of hypoparathyroidism, the operative failure rate and the chance of developing recurrent HPT are slightly higher [22].

Secondary Hyperparathyroidism

Data regarding intraoperative PTH monitoring in patients with secondary HPT are limited and difficult to evaluate due to the heterogenicity of the populations studied. The operative findings in patients with secondary and tertiary HPT are often evaluated together and the results of patients on dialysis are combined with the ones that underwent renal transplantation. This heterogenicity decreases the credibility of the results of IPM guided resection in patients with renal failure. Also the accuracy of the various criteria in predicting operative success is difficult to compare since the expected outcomes are different among these studies. Some investigators considered a successful parathyroidectomy when patients have a PTH level within normal range for at least 6–12 months while others use the PTH as high as four times the normal range as the goal for a successful operation [15–18]. Table 18.4 shows the accuracy of various criteria to predict complete excision in patients with secondary HPT. The use of whole intact molecule or Bio Intact PTH seemed to be promising in guiding parathyroidectomy in secondary HPT, but it is currently not available in this country [16].

The usefulness of IPM and which criteria to be used in patients with secondary HPT have not been well established. Studies that have a homogenous population, strict and consistent intraoperative PTH criterion, and long-term follow-up might eventually demonstrate the benefit of using IPM in the treatment of patient with secondary HPT on continuous dialysis.

Tertiary Hyperparathyroidism

The use of IPM in patients with tertiary HPT was previously described by Chen and Richards [14, 17]. In some of these patients, intraoperative information on the PTH dynamics was described only after all parathyroid glands were excised with no blood samples collected

after each gland resection. It is unknown if all the number of parathyroid glands that are autonomously hyperfunctioning in hypercalcemic patients after kidney transplantation is unknown. Patients with secondary HPT have multiple metabolic imbalances resulting in oversecretion of parathormone by all parathyroid glands. When these stimuli of chronic hypocalcemia, hyperphosphatemia, and low vitamin D are resolved, it is unknown if all parathyroid glands are actually autonomously hypersecreting in patients with tertiary HPT. Chen and Richards, in two separate studies, have answered this question when they described an incidence of 9–33% of single gland disease determined by the IPM in patients with tertiary HPT [14, 17]. Conversely, Chen et al. suggested that a BNE should be done routinely due to the high incidence of MGD. Richards et al., on the other hand, used IPM to guided parathyroidectomy in these patients and found that IPM with the >50% drop was as accurate in predicting operative success in tertiary HPT as they are in SPHPT. The incidence of single glandular involvement is very low, but was correctly predicted by IPM in the majority of the cases [14].

Parathyroid Cancer

The results of parathyroidectomy guided by IPM in patients with parathyroid cancer are rarely described. In our experience, the incidence of false-positive results are higher in patients with cancer than in SPHPT [23]. We believe that the tumor biology causing regrowth of the cancer before 6 months is the reason for the false-positive results not necessarily missed MGD. Even though IPM is accurate in pointing out insufficient resection during reoperations, it is not as accurate in predicting operative success during initial parathyroidectomies as it is in SPHPT. IPM sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy in predicting outcome in parathyroid cancer are 100, 40, 70, 100, and 75%, respectively. In patients with parathyroid cancer, intraoperative PTH values are not as accurate in predicting complete excision, making the initial recognition of malignancy with en bloc resection paramount for the treatment of these patients [23].

Multiple Endocrine Neoplasia

The use of IPM to guide the excision in patients with MEN1 was reported by Tonelli et al. [19]. They described a 16-year experience of surgical treatment of MEN1 patients using total parathyroidectomy, thymectomy, and autotransplantation. In this study, a drop in the PTH level to <10 pg/ml at the end of the procedure indicated total parathyroidectomy and that autotransplantation should be done. IPM was also helpful in the excision of hyperfunctioning grafts causing recurrence and the drop of 50% in the PTH level 10 minutes after the excision of the hyperplastic tissue predicted successful resection.

Summary

IPM has changed the management of patients with SPHPT. The use of this surgical adjunct has become a standard of care in the treatment of SPHPT by most endocrine surgeons.

IPM can be used with several intraoperative criteria and blood sampling times, but in our experience, the "$>$50% PTH drop" criterion that includes a >50% peripheral PTH drop, from the highest either preincision or preexcision level, 10 minutes after the excision of a suspicious gland predicts the operative outcome with an overall accuracy of 98%. We recommend using the preincision and preexcision levels in all operations in an attempt to increase the accuracy of the IPM and criteria by decreasing FN results. If the surgeon wants to use stricter criteria to decrease false-positive results therefore preventing missed MGD, the drop of PTH to normal range will achieve this goal; on the other hand, it will lead to a significant increase in the incidence of FN results with excision of normally secreting glands.

The use of IPM has proved to be accurate in patients with SPHPT and isolated familial HPT, but its accuracy is questionable in patients with secondary, tertiary HPT, parathyroid cancer, and MEN syndrome. Further studies are needed to prove the usefulness of this surgical adjunct in these patients.

Despite the recognized limitations, IPM using the "$>$50% PTH drop" criterion is very

helpful to the surgeon intraoperatively and has become a valuable tool in the treatment of hyperparathyroidism.

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19

Focused Parathyroidectomy

Johan Westerdahl and Anders Bergenfelz

Background

The parathyroid glands were first described in 1880 by the Swedish anatomist and medical student Ivar Sandström. He named them "glandula parathyroideae." In 1908 the association between serum calcium and the parathyroid glands was established by MacCallum and Voegtlin [1].

The first successful parathyroidectomy was performed in 1925 by Felix Mandel in Vienna on a patient with severe osteitis fibrosa cystica [2]. During the early days of parathyroid surgery removal of one large gland was usually successful. However, the concept of chief cell hyperplasia was established in 1958 by Cope [3], and with the recognition of primary parathyroid hyperplasia as a distinct histopathologic entity, it became obvious that in a proportion of patients with primary hyperparathyroidism (pHPT) more parathyroid tissue had to be removed [4]. Since it was not possible to distinguish between uniglandular and multiglandular disease without identifying all parathyroid glands, bilateral exploration was advocated.

Evolution of Surgery for pHPT

Bilateral neck exploration, with identification of at least four parathyroid glands and removal of all enlarged glands yields excellent results [5, 6] and has over the years evolved as the gold standard for the surgical treatment of pHPT. With the introduction of autoanalyzers in clinical chemistry during the 1970s the diagnosis of pHPT has become more frequent. The symptoms of pHPT patients today bear little resemblance with the severe disorder of the bones and the kidneys described by Albright in the 1930s [7]. Contemporary patients are typically elderly women, with mild aberrations in serum calcium and associated cardiovascular comorbidity is common [8]. In response to the more frequent diagnosis of pHPT surgery has over the past 20 years evolved rapidly worldwide [9].

It is known that up to 90% of patients with pHPT have a solitary adenoma [10, 11]. In these patients only one gland requires excision for cure. A bilateral surgical approach is associated with postoperative hypocalcemia in up to 15% [12]. To simplify the surgical procedure and reduce the risk of postoperative hypocalcemia the concept of limited parathyroid exploration was first suggested by Wang in the 1970s [13]. He used intraoperative oil red O staining and the saline float test to help determine whether a parathyroid gland was normal. Later the unilateral approach was refined by Tibblin [14], who thereby started the new era of parathyroid surgery.

Open Unilateral Neck Exploration (Original approach)

The unilateral approach has no place in the management of patients with multiple endocrine neoplasia (MEN1 and MEN2) and familial

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hyperparathyroidism since these conditions by definition have a multiglandular involvement. Previous parathyroid or thyroid surgery is generally a contraindication.

The technique was introduced in our department in 1977 by Tibblin. The main principle of the unilateral technique is to restrict the operation to the side on which the solitary adenoma is located. Originally no preoperative localization study was used. Surgery was performed through a short (<5 cm) standard Kocher incision, with the strap muscles separated in the midline and not divided. If an adenoma was found on the first side, then both the adenoma and the normal appearing gland were removed and the procedure was terminated. If the adenoma was not found, the two normal parathyroid glands were left in situ and the contralateral side explored, removing both the adenoma and the normal gland on the second side. The diagnosis was confirmed with the help of intraoperative frozen section. Oil red O staining of parathyroid tissue, introduced by Roth and Gallagher [15] and later modified by Ljungberg and Tibblin [16] was used to distinguish between normal and abnormal parathyroid tissue as well as between adenoma and hyperplasia. Typically, suppressed chief cells are stained whereas adenomatous cells do not stain. The distinction between a solitary adenoma and a hyperplastic gland remains controversial for some pathologists since they believe it is not possible to differentiate between an adenoma and a hyperplastic gland without a histological comparison with a normal gland. The presence of a suppressed rim of normal parathyroid tissue aids the diagnosis of an adenoma. Since this tissue usually is located where the vessels enter the gland, the surgeon can help the pathologist by marking the vascular pedicle.

From the beginning, the unilateral approach has yielded good results with a reduced risk of hypocalcemia [17–20] and vocal cord injury [19]. A systemic review, undertaken a few years ago, comparing unilateral with bilateral neck exploration indicated a tendency to favor the unilateral approach [21]

The unilateral technique has been modified with the advent of improved preoperative localization and measurement of intraoperative parathyroid hormone (ioPTH). Thus, the modern method for unilateral exploration is as follows: If an adenoma is found on the first side explored, it is excised. If the adenoma is not found or the result of ioPTH measurement is inconclusive (see below), comprehensive bilateral exploration is performed. The exploration always starts on the side indicated by the preoperative localization. When preoperative localization is negative, the exploration always starts on the same side, e.g., the left side. No attempt is made per se to visualize normal glands. Frozen section is not used.

This modified unilateral approach has recently been compared with conventional bilateral neck exploration in a prospective randomized trial [22]. Unilateral neck exploration demonstrated a lower incidence of biochemical and severe symptomatic hypocalcemia, most marked in patients with a solitary adenoma. Cost and long-term cure did not differ between techniques [22, 23].

Preoperative Localization

As solitary adenomas are equally distributed in the neck, about 50% of patients would undergo a unilateral neck exploration without the use of preoperative localization, provided this was always started on the same side [17]. However, for a higher success rate in focused parathyroid surgery, preoperative localization studies with a high accuracy are required. When comparing the accuracy between different modalities and studies it is important to consider the characteristics of the patients under study, particularly adenoma size, PTH values, and concomitant thyroid disease. We advocate the use of preoperative localization studies in patients with previous thyroid or parathyroid surgery and in patients planned for focused parathyroid surgical techniques.

Sestamibi-technetium scintigraphy has emerged as the noninvasive localization procedure of choice [24–27]. Previous studies have reported sensitivity of up to 90% [28–30]. However, a recent meta-analysis has shown wide differences in reported sensitivity [31]. Furthermore, an audit from the Scandinavian quality register for parathyroid surgery reported a modest sensitivity of only 64.4% [32]. A further concern is the inability of the technique to predict multiglandular disease [28, 33, 34]. The sensitivity of sestamibi scintigraphy may be improved by the addition of delayed imaging based on differential washout kinetics [35], single photon emission computed tomography

(SPECT) [36], or oblique views with higher dose [37]. This remains to be proven in prospective trials.

Ultrasonography (US) has become one of the preferred preoperative localization techniques. US is operator and equipment dependent, and accordingly the reported sensitivity varies widely in the literature [38–40]. The importance of the combination of skill, experience, and interest, was shown in a study comparing surgeon-performed with radiology-performed US [41]. Surgeon-performed US had the best accuracy, and it has been suggested that surgeon-performed US, which has the advantage of being a cheap, noninvasive, and comparatively sensitive investigation, should be the initial localizing test [42]. With the addition of fine-needle aspiration and PTH sampling the precision of US may approach 100% [43].

Computed tomography and magnetic resonance imaging are superior to US in identifying ectopic parathyroid glands but normally has no role in the management of pHPT patients prior to initial surgery.

Both [18F]-Fluoro-2-deoxy-D-glucose (FDG) [44] and [11C]-methionine [45] positron emission tomography (PET) have been used to localizing parathyroid glands. However, PET is not routinely available at most institutions and the cost is high, it is considered an option only when other localization modalities have failed in reoperative situations. Selective venous sampling and PTH measurement can be used for preoperative [46] localization in reoperative surgery, or intraoperative [47] localization as an aid to the surgeon.

Intraoperative Measurement of PTH

In recent years, the intraoperative measurement of PTH (ioPTH) has become an adjunct to parathyroid surgery for pHPT. This means a shift from a gross morphological definition to a biochemical definition of a hyperfunctional parathyroid gland. A method for intraoperative measurement of intact PTH was developed in the late 1980s by Nussbaum [48]. To shorten the time for intraoperative analysis, the assay was modified, enabling the incubation time to be shortened to about 15 min. Subsequently other groups have adopted the idea and developed techniques for ioPTH measurement [49–52]. Today the turnaround time has become even shorter since the analysis is performed in the operating room by laboratory personnel [53].

The basic concept of ioPTH measurement is straightforward. It is based on the fact that PTH in plasma has a short half-life of about 3–5 min. Therefore, it is possible to detect a significant drop in plasma PTH following the excision of a parathyroid adenoma. When an enlarged parathyroid gland is excised and there is no significant decrease of ioPTH, multiglandular disease must be suspected and a comprehensive bilateral exploration undertaken.

We have used ioPTH since the early 1990s. We obtain our samples from a peripheral vein according to a strict protocol [51]. Since parathyroid manipulation may affect the PTH value, it is important that meticulous dissection is performed without pressure on the parathyroid, before the vessels are ligated or clipped. The baseline, preexcision sample should be obtained when the enlarged gland is first visualized. In our opinion it is important that samples are obtained from a peripheral vein and not the jugular veins because the latter will be more affected by the manipulation of the enlarged gland. Furthermore, a parathyroid adenoma, whether up- or downstream from the sample site will influence the PTH level differently. Second and third samples are collected 5 and 15 min after excision, respectively. In our hands the efficacy of the method relies on a decline of ioPTH at 15 min of $>$60% of baseline [51]. If this criterion is fulfilled ioPTH reliably predicts a solitary adenoma with an excellent early as well as a late operative success [54]. The Miami group and others successfully use a decrease in ioPTH of $>$50% at 10 min as a criterion to terminate neck exploration [55–58]. This criterion has become the most widely used to predict cure in patients with sporadic pHPT (but is not suitable for patients with other causes of HPT). However, it is important to realize that modifications of the technical aspects of ioPTH and the applied criterion have a significant impact on the overall accuracy of the test [59]. It is interesting to note that the reported proportion of patients with multiglandular disease is considerably lower in series using focused approaches combined with ioPTH measurement, i.e., a biochemical definition of a hyperfunctional gland, compared to

series where bilateral exploration was performed using a gross morphologic definition of a hyperfunctional gland (5 vs 20% multigland disease) [60]. Critics have expressed concern that enlarged hyperfunctioning glands may be left in situ leading to higher failure rates in terms of persistent and recurrent disease [60]. This concern is largely based on studies where, during bilateral exploration, a number of patients have a remaining enlarged gland following the excision of the hyperfunctioning gland, confirmed by a >50% decline in ioPTH [61]. However, because these enlarged glands were also removed it is not known whether if left in situ, they would have caused persistent or recurrent disease. To date, the reported long-term results support a biochemical definition of a hyperfunctional parathyroid gland in sporadic pHPT [23, 54].

Several studies have reported that ioPTH has a proportion of false-positive results, i.e., a sufficient decline in ioPTH post excision of a solitary gland despite the presence of multiglandular disease [55, 57, 58]. In our experience this is a rare phenomenon provided a strict protocol, as outlined above, is followed. Among late surgical failures with false-positive ioPTH findings, multiple endocrine neoplasia (MEN1) should be suspected [54].

In the new era of focused parathyroid surgery, the rate of false-negative ioPTH findings represents a special problem, because these findings usually lead to conversion to an open bilateral procedure. Ideally this rate should be as low as possible. It has been shown that a preincision sample, at the induction of anesthesia, in addition to the preexcision sample can reduce the rate of false-negative findings, when the decline is calculated from the highest of these values [59]. Occasionally a false-negative finding is caused by a delayed drop in ioPTH. A further sample >15 min post excision may be valuable in such cases.

Recently it has been suggested that successful focused surgery could be achieved without the use of ioPTH when two preoperative localization studies (US and sestamibi scintigraphy) show concordant imaging of a solitary adenoma [62, 63]. However, this occurs in only about 50% of cases. Others have recommended from a cost-benefit reason that same-day PTH testing is better than ioPTH measurement [64], especially in patients with an unequivocal single lesion on sestamibi scanning [65]. Still others have suggested that PTH measurement should only be undertaken the morning after surgery [66]. In most hands sestamibi scintigraphy does not reliably predict multiglandular disease [28, 33, 34], and the sensitivity is dependent on gland size and concomitant thyroid disease [67]. Therefore ioPTH measurement is recommended as an adjunct to predict the postoperative outcome if focused parathyroidectomy is not to be restricted to a highly selected group of patients with an unequivocal sestamibi scan, or with two localization studies showing a concordant solitary location. Strictly speaking, the role of ioPTH in terms of success rate and cost-benefit remains to be proven in prospective randomized studies.

Methylene Blue Dye

Intravenous administration of methylene blue for the rapid identification of parathyroid tissue was first proposed by Dudley in 1971 [68] and is today used by some surgeons as an intraoperative aid. Methylene blue (methylthionine chloride) is administered intravenously as an infusion, at a calculated dose of 5 mg/kg body weight in 500 ml normal saline, preoperatively after induction of anesthesia. Parathyroid adenomas and hyperplastic glands are turned dark blue to purple, while normal glands are stained to a lesser degree, or not at all. The color of the parathyroid glands is described to progressively increase in intensity after the infusion for up to 1 h and seems to last for 20 min before diminishing in intensity over the next 2½ h [68]. It is important to inform the anesthesiologist of the pseudocyanotic pallor that the patient develops during surgery and for some hours postoperatively as a consequence of the infusion. The mechanism behind the parathyroid tissue staining is unknown. Several groups have subsequently reported the method to be safe and effective in localizing abnormal parathyroid glands [69, 70] and to considerably shortening the operating time [71]. The method is also useful in persistent and recurrent hyperparathyroidism [72]. Although the method is generally considered to be safe with insignificant levels of methemoglobinemia, recently there have been some case reports of prolonged mental disorientation after methylene blue infusion [73, 74]. At our institution we have found that a calculated dose of 2.5 mg/kg body weight in

500 ml saline given as an infusion under 40 min is as effective in staining abnormal parathyroid glands as the widely used dose of 5 mg/kg body weight and we have not so far encountered any troublesome side effects.

Radioguidance

Radioguided parathyroidectomy was first described by Martinez et al. in 1995 [75]. The technique has thereafter been further developed for focused surgery by others [76, 77]. Technetium 99m-sestamibi is injected intravenously 2–4 h prior to surgery, and the radiolabeled parathyroid gland is then intraoperatively localized with the help of a handheld gamma probe. The anterior portion of the neck is scanned and the site with highest counts is explored using the probe as a guide toward the abnormal parathyroid gland. An excised parathyroid adenoma should contain more than 20% of the postexcision background radioactivity [78]. The technique reduces operative time [37] and can be performed in a focused fashion without ioPTH measurement [79]. Although the technique has been further refined, validated [78, 79], and shown to be useful in reoperative cases [80], at present only a minority of endocrine surgeons throughout the world have adopted the gamma probe radioguidance approach. It is widely believed that the technique adds little additional information to the initial preoperative sestamibi scan and ioPTH measurement. However, there is no prospective randomized study on the subject.

Local/Regional Anesthesia

Most commonly parathyroid surgery is performed under general anesthesia. However, it can also be performed under local/regional anesthesia. Parathyroidectomy under local anesthesia was initially proposed for the elderly high-risk patient [81, 82]. It is well tolerated and blood pressure as well as heart rate fluctuate less than in general anesthesia [82]. In recent years it has been suggested that local/regional anesthesia should be considered for focused parathyroid surgery techniques in most patients with sporadic pHPT and a localized adenoma [83–85]. This approach is claimed to reduce operating time and be well suited for ambulatory cases [86]. Local anesthesia is generally given as an infiltration along the line of incision in combination with mild intravenous sedation and/or intravenous analgesics. Regional anesthesia is usually performed as a cervical block, sometimes in combination with a mild intravenous sedation. The cervical block can be administered in three stages [87]. First, a superficial cervical block is placed deep and posterior to the sternocleidomastoid muscle on the ipsilateral side. Second, it is supplemented by infiltrating the anterior border of the sternocleidomastoid muscle. Finally, a local infiltration is made along the line of the incision. Bilateral neck exploration can be accomplished with cervical block.

Focused/Minimal Invasive Parathyroidectomy

Overview

During the last 10–15 years the surgical treatment of pHPT has radically changed, due to improvement in preoperative localization studies, ioPTH assessment, and introduction of new surgical techniques, open as well as video-assisted. The unilateral technique performed through a short (<5 cm) standard Kocher incision has been abandoned in favor of less-invasive techniques. However, from a principle point of view the main difference is still between unilateral and bilateral neck exploration. Most new focused techniques rely on ioPTH measurement in contrast to the bilateral technique which uses gross morphology and frozen sections, i.e., the two approaches define a hyperfunctioning parathyroid gland differently: a biochemical definition versus a gross morphological definition.

Focused or minimally invasive parathyroidectomy encompasses a number of different techniques such as open approaches [85, 88], video-assisted parathyroidectomy [89–91], and radioguided parathyroidectomy [76, 77] (Fig. 19.1). Although there is no strict definition of minimal invasive parathyroidectomy the term is commonly used for the removal of a localized abnormal parathyroid gland through an incision of less than 3 cm in length. The term is used interchangeably with focused parathyroidectomy. Patients are usually discharged on the same day or after an overnight stay.

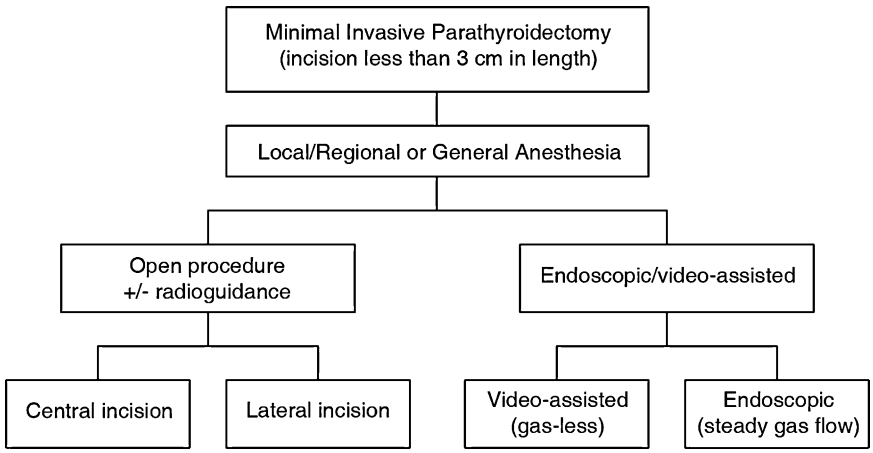

Fig. 19.1. Schematic view of different techniques in minimal invasive parathyroid surgery.

A prerequisite for the different focused techniques is a precise understanding of the anatomical details of normal as well as abnormal parathyroid glands and their relationship to anatomical landmarks in the neck. Furthermore, these focused approaches require the abnormal parathyroid to be preoperatively localized.

Several reports have demonstrated the feasibility of the concept of focused parathyroidectomy [65, 86, 92, 93]. Most of these studies suggest that the new focused techniques are safe, and as least as good as standard bilateral exploration, but with some advantages (less postoperative hypocalcemia, shorter operating time, early discharge, and perhaps better cosmesis and less postoperative pain). In addition, there are six randomized controlled trials with short-term results [22, 94–98] and one with long-term results [23] that suggest some distinct benefits for focused parathyroid surgery (see section below on Evidence-Based Medicine in Parathyroid Surgery).

There has been a global trend toward the acceptance amongst endocrine surgeons for these focused approaches [9]. However, an audit from the Scandinavian quality register for parathyroid surgery showed that bilateral neck exploration is performed in two thirds of all pHPT operations [32].

Open-Focused/Minimal Invasive procedures

Open-focused parathyroidectomy is typically done through a small lateral or central neck incision. When using the lateral approach, a 2- to 3-cm lateral incision is placed transversally directly over the site of the adenoma and overlying the anterior border of the sternocleidomastoid muscle [88]. With the sternocleidomastoid muscle retracted laterally and the strap muscles medially, a subplatysmal space is created down to the prevertebral fascia and the posterior aspect of the thyroid gland – the parathyroid-bearing region. After the enlarged gland is identified, it is excised and its vascular pedicle ligated or clipped.

Other groups advocate a central approach [85, 99]. A 2- to3-cm abbreviated Kocher skin incision is made 2 cm above the sternal notch. The strap muscles are divided in the midline and retracted laterally. The ipsilateral thyroid lobe is mobilized and the parathyroid adenoma is identified, its vascular supply ligated or clipped, and the parathyroid is removed.

Both techniques can be undertaken under general or regional anesthesia.

The open-focused technique can also be combined with the use of a gamma probe for radioguidance (see also section Radioguidance).

Endoscopic/Video-Assisted Procedures

Technical progress in laparoscopy and endoscopy has in recent years also been introduced in the field of parathyroidectomy. The first endoscopic parathyroidectomy was reported in 1996 by Gagner [100]. The operation was in

many ways not a success since it took 5 h and was complicated by intraoperative hypercarbia and postoperative severe subcutaneous emphysema [101]. However, several other techniques have subsequently been developed and variations of the procedure include endoscopic (with steady gas flow) as well as video-assisted (gasless) approaches.

Typically, the access for the endoscope is obtained centrally above the sternal notch and the exploration is carried out with two instruments introduced through two additional trocars at the anterior border of the sternocleidomastoid muscle on the side of the localized adenoma. A variant of this strategy is the video-assisted parathyroidectomy by lateral approach (VAPLA) described by Henry [102]. VAPLA is performed on the line of the anterior border of the sternocleidomastoid muscle. A 12-mm transverse skin incision is made on the anterior border of sternocleidomastoid muscle, about 1 cm caudal to the cricoid cartilage. Through this incision a working area is created between the prevertebral fascia and the posterior portion of the strap muscles and the thyroid lobe. Two 2.5 mm trocars are inserted on the line of the anterior border of sternocleidomastoid muscle. A 10-mm trocar for the 0° endoscopic camera is inserted through the initial incision. Carbon dioxide is continuously insufflated. The video-assisted exploration is carried out with 2-mm instrument. When the adenoma is completely dissected, the trocars are removed and the adenoma is extracted directly through the skin incision after clipping its vascular pedicle.

One of the most well-documented video-assisted methods was introduced by Miccoli [89]. This procedure, which relies on external retraction and not gas insufflation, is characterized by a single 1.5-cm transversal skin incision about 2 cm above the sternal notch. The cervical linea alba is divided longitudinally, and the strap muscle on the side of the adenoma is dissected from the thyroid lobe. Originally the operative space was created by a brief insufflation of carbon dioxide [89]. The gas insufflation has later been abandoned, and the space is currently recommended to be generated by gentle blunt dissection under direct vision [92]. For the dissection of the parathyroid gland 2-mm instruments are used and a 30° 5-mm endoscope for magnification. Once identified, the parathyroid gland is carefully handled, vascular supply clipped, and the gland excised. No attempts are made to visualize normal parathyroid glands. Some advantages with this method are that a bilateral exploration can be performed through the same skin incision and that the method can also be used for thyroid operations. The method can be undertaken under general anesthesia as well as under regional anesthesia [98].

An entirely different endoscopic approach, the axillary approach, has been reported by Ikida [103]. This procedure requires extensive dissection and in that sense does not belong to the minimal invasive arsenal.

Evidence-Based Medicine in Parathyroid Surgery

Level of evidence in evidence-based medicine is frequently used for the recommendation of specific treatments. A well-conducted prospective randomized trial is assigned the highest level of evidence. A problem with endocrine surgery in general and focused/minimal invasive parathyroid surgery in particular, is that prospective randomized studies are rare.

To date six randomized controlled trials with short-term results [22, 94–98] and one with long-term results [23] have been published (Table 19.1). Only one of these studies was designed as an unselected randomized trial, with randomization performed before sestamibi scintigraphy. Scintigraphy was only performed in patients randomized for unilateral surgery [22]. The study was analyzed on an intention to treat basis and results showed a lower incidence of biochemical and symptomatic early hypocalcemia, and a shorter operating time for patients with unilateral exploration compared to bilateral exploration. There was also a tendency toward a lower overall complication rate in the unilateral group. Early as well as late surgical outcomes were similar for both groups [22, 23].

Three other trials have compared focused parathyroid exploration with conventional bilateral neck exploration among pHPT patients with preoperatively localized abnormal parathyroid gland [94, 96, 97]. In the first of these three studies, open-focused parathyroidectomy under local anesthesia was compared to bilateral neck

Table 19.1. Randomized controlled trials on parathyroid surgery

Study	Location	Year	Patient Number	Randomization	Follow-up Months	Results
Bergenfelz et al. [22]	Sweden	2002	91	Unilateral vs bilateral neck exploration	1.5	Lower incidence of biochemical and severe symptomatic hypocalcemia in unilateral group. Reduced operating time in unilateral group
Westerdahl et al. [23]	Sweden	2007	88/71	Unilateral vs bilateral neck exploration	60	Same long-term results
Bergenfelz et al. [94]	Germany	2005	50	Bilateral vs open minimal invasive surgery under local anesthesia	6	Less biochemical hypocalcemia and reduced operating time in open minimal invasive group
Barczynski et al. [95]	Poland	2006	60	Video-assisted vs open minimal invasive parathyroidectomy	6	Less pain and need for analgesia, shorter scar, better physical functioning, and cosmetic result, but higher costs in video-assisted group
Russel et al. [96]	Northern Ireland	2006	100	Scan-directed unilateral vs bilateral cervical exploration	23	No difference in results between the two groups
Miccoli et al. [97]	Italy	1999	38	Video-assisted vs bilateral neck exploration	6	Shorter operating time, less pain, and better cosmetic result in video-assisted group
Miccoli et al. [98]	Italy	2005	51	Regional vs general anesthesia in video-assisted parathyroi dectomy	20	Shorter operating time and reduced pain with regional anesthesia

exploration [94]. Patients in the focused surgical group had a shorter operating time and less biochemical hypocalcemia with no difference in cure rate. The second study compared video-assisted parathyroid surgery with bilateral neck exploration [97]. The study was done without a power-calculation. It found less pain, better cosmesis, shorter operating time, and less hypocalcemia in the video-assisted group. In the third study, scan-directed parathyroidectomy and bilateral neck exploration were found to have the same cure rate [96]. Only patients with a positive scan and a preoperative single tumour at the same site were included, and preoperatively randomized to unilateral or bilateral exploration. The trial did not use ioPTH.

In a study from Poland video-assisted parathyroidectomy has been compared with open-focused parathyroidectomy [95]. The study suggested some advantages in early recovery, less

postoperative pain, and shorter scar in the video-assisted group. However, the video-assisted technique was more expensive.

Finally, one Italian study has assessed video-assisted parathyroidectomy performed under general or regional anesthesia [98]. The use of regional anesthesia showed some benefits in terms of shorter operating time and less pain.

In conclusion, these randomized studies suggest that focused parathyroidectomy can offer some advantages compared with bilateral neck exploration in terms of reduced rate of postoperative hypocalcemia, shorter operating time, and possible also less pain and better cosmesis, with no difference in cure rate. However, an evaluation of the policy of early discharge has thus far not been addressed in a randomized controlled study. There is also a need for more studies presenting long-term results.

Conclusion and Future Aspects

Focused parathyroid surgery for patients with sporadic pHPT is here to stay. It is the ideal surgical treatment of patients with a single parathyroid adenoma. However, it is important for new surgical techniques, preoperative localization procedures, and ioPTH monitoring to be more thoroughly evaluated. Preferably, this evaluation should be achieved, through open audit of large patient cohorts from different types of institutions and through well-designed multicenter randomized trials.

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20

Parathyroid: Bilateral Neck Exploration

Takahiro Okamoto and Takao Obara

Introduction

Endocrine surgeons have continued to dispute over the appropriate extent of surgery for primary hyperparathyroidism, namely bilateral versus unilateral neck exploration [1–10] (Table 20.1). Since the first successful operation by Felix Mandl in 1925, bilateral neck exploration has been the standard approach to the disease in order to avoid overlooking any functioning parathyroid lesions that may lead to persistent or recurrent hyperparathyroidism. The necessity of this approach, however, has been challenged because over 80% of the patients have a single parathyroid adenoma where a simple removal will suffice to cure the disease. Wang and Tibblin have advocated that only one side of the neck be explored given an adenoma and normal gland are found on the same side with the aid of intraoperative assessment such as a density test or oil-red-O staining of frozen sections [4–5]. Subsequent developments of preoperative localization modalities, namely high-resolution ultrasonography and ^{201}Tl-^{99m}Tc subtraction scan or ^{99m}Tc sestamibi scan, have enabled endocrine surgeons to perform unilateral neck exploration with greater confidence so that the routine bilateral inspection is unnecessary. In addition, the emergence of an intraoperative measurement of parathyroid hormone facilitated the adoption of a focused approach based on preoperative localization to confirm surgical success and identify the presence of residual hyperfunctioning parathyroid tissue [6]. Although experienced endocrine surgeons still advocated a bilateral approach in the early 1990s [8–9], and in fact a worldwide questionnaire survey by Tibblin et al. in 1991 revealed that 82% of the surgical departments were still exploring bilateral neck [10], a 2002 survey by Sackett et al. disclosed that 59% of the respondents performed minimally invasive parathyroidectomy (MIP) on average for 44% of patients with primary hyperparathyroidism [11].

In this chapter, the role of bilateral neck exploration as a treatment of sporadic primary hyperparathyroidism in the era of focused approach is discussed. This approach is also essential for hyperparathyroidism due to multiple endocrine neoplasia and renal failure but would be discussed elsewhere.

Bilateral Neck Exploration: What are we Talking About?

Bilateral neck exploration, once recommended as a standard operative procedure for primary hyperparathyroidism, includes identification of all four glands, removal of enlarged one, and biopsy of three normally appearing glands [11]. This classical approach, however, has not necessarily been used by endocrine surgeons because it was found to be associated with frequent postoperative hypocalcemia,

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Table 20.1. Development and evolution of surgical treatment of primary hyperparathyroidism

	Development	Bilateral neck exploration	Unilateral neck exploration	Focused parathyroidectomy
1920s	• Mandl F: First successful operation in Austria.			
1930s	• Mandl F: Recurrence of the first case • Cope O: Successful removal of a adenoma in the mediastinum after several failed neck explorations	Walton AJ: "always exposure all the parathyroid glands, sometimes search behind the trachea and the mediastinum"		
1940–60s				
1970s	• Ultrasonography • Computerized tomography • A density test of resected tissue		Wang CA: "only if an adenoma is found on the first side and the other gland is normal"	
1980s	• High-resolution ultrasonography • ^{201}Tl-^{99m}Tc subtraction scan • oil-red-O staining of frozen sections		Tibblin S: "it is not necessary to explore all four glands"	
1990s	• NIH Consensus for asymptomatic cases • ^{99m}Tc-sestamibi scan • intraoperative quick PTH measurement • Prospective studies of unilateral neck exploration	Kaplan EL: "strongly recommend a bilateral exploration for all patients" Proye CAG: "routine bilateral neck exploration is recommended"	Russell DFJ: "scan-directed unilateral neck exploration is a legitimate alternative"	Irvin GL: limited parathyroidectomy guided by intraoperative quick PTH measurement Gagner M: endoscopic parathyroidectomy
2000s	• Randomized controlled trials of bilateral versus unilateral or focused neck exploration			

NIH: National Institute of Health

especially when excessive biopsies of normal glands were performed [12]. In the survey by Tibblin, surgeons were rather conservative in intraoperative evaluation of normal-sized parathyroid glands, and only nine respondents performed the classical procedure among 43 surgical departments where bilateral neck exploration was routinely performed [10] (Table 20.2). Thus it is important to note that what "bilateral neck exploration" means may differ among endocrine surgeons with regard to the extent of intraoperative evaluation techniques and the use of preoperative localization tests.

Table 20.2. Questionnaire survey on surgical procedures for primary hyperparathyroidism due to single parathyroid adenoma reported in 1991

Neck exploration	Biopsy of normally appeared glands	Respondents
Bilateral	Excisional biopsy of one gland	7 (13%)
	Incisional biopsy of three glands	9 (17%)
	Incisional biopsy of one to two glands	16 (31%)
	No biopsy	11 (21%)
Unilateral	Excisional biopsy	6 (12%)
	Incisional biopsy	3 (6%)
		52 (100%)

Source: Data from [10].

Bilateral Versus Unilateral Neck Exploration: The Evidence

Systematic Review

Reeve et al. conducted a systematic review of the literature to compare the outcomes of minimally invasive surgery (either unilateral or focused) with those of bilateral neck exploration [13]. The authors, however, faced difficulty in drawing solid conclusions for the efficacy and safety of minimally invasive surgery because the selected studies differed in study designs, study populations, preoperative localization tests, surgical interventions, and outcomes [13–22] (Table 20.3).

Prospective, Quasi-Experimental Studies

Based on a prospective, multicenter study where five different surgical regimens for patients with primary hyperparathyroidism due to solitary adenoma were compared, Tibblin and his colleagues found that severe postoperative hypocalcemia was significantly more common after bilateral than unilateral exploration [23] (Table 20.4). They also concluded that unilateral parathyroidectomy without contralateral inspection were no more likely to cause persistent or recurrent hypercalcemia than bilateral approach, given the diagnosis of single gland disease was confirmed by the use of intraoperative fat staining. Other five prospective studies on unilateral neck exploration (not focused approaches) are summarized in Table 20.5. Russell and his colleagues pioneered in adopting the scan-directed unilateral neck exploration where contralateral side was also explored if preoperative ^{201}Tl-^{99m}Tc scanning was negative or the unilateral approach failed to identify the parathyroid lesion [24]. Of the 90 patients in the study, 48 (53%) had unilateral surgery while the rest actually needed bilateral exploration. Among 46 patients with unilateral approach whose data were available at mean follow-up of 16.8 months, no one demonstrated persistent or recurrent hypercalcemia. Since hypercalcemia did not resolve in 6 of 42 individuals undergoing bilateral exploration, the overall success rate of this strategy was 93%. Later, the investigators retrospectively reviewed the long-term outcome of 184 patients in whom cervical exploration was limited to one side [25]. Following the initial operation three patients (1.6%) demonstrated persistent hypercalcemia while none of the cured patients had developed recurrent disease at mean follow-up of 59 months. Wei and Burke examined if preoperative radiologic localization with unilateral neck exploration reduced operative time compared with full bilateral neck exploration. They observed that unilateral neck exploration provided 100% cure and would save approximately 30 min in completing curative surgery [21]. Norman et al. also reported 100% cure rate of unilateral neck exploration with a study population of primary hyperparathyroidism patients with a solitary adenoma detected by preoperative ^{99m}Tc sestamibi scanning [17]. Carty

Table 20.3. Studies included in the systematic review of unilateral and bilateral neck exploration for primary hyperparathyroidism

Author	Study design	Study population	Preoperative imaging	Intervention	Outcomes
Vogel [14]	Retrospective	106 PHPT	US (93), MIBI (17)	UNE > BNE	IS, OT, OS, AE
Denham [15]	"meta-analysis"				Performance of MIBI OT, C, P
Ryan [16]	"Case-control"	100 sporadic PHPT	US (93), Tl-Tc (84)	UNE versus BNE	IS, OT, OS, AE
Norman [17]	Prospective (with historical controls)	18 PHPT with MIBI positive (25 PHPT as historical controls)	MIBI (18) vs no tests (25)	UNE versus BNE	IL, OT, HS, OS, AE
Vroonhoven [18]	Prospective	66 PHPT	US and CT	Minimal > BNE	OT, OS, AE
Tsukamoto [19]	Not declared.	160 PHPT	Tl-Tc	UNE > BNE	IS, OT, OS
Petti [20]	Retrospective	100 PHPT	Tl-Tc (50) vs. no tests (50)	UNE versus BNE	OT, OS, AE, C, HS
Wei [21]	Prospective	33 PHPT with MIBI positive indicating a solitary adenoma.	MIBI	UNE + contralateral neck exploration	OT
Worsey [22]	Retrospective	371 sporadic PHPT	US (22), Tl-Tc (24), both (29), no tests (275)	UNE > BNE	OS, OT, AE

PHPT: primary hyperparathyroidism, MIBI: ^{99m}Tc-sestamibi scan, Tl-Tc: ^{201}Tl-^{99m}Tc subtraction scan, US: ultrasonography, CT: computed tomography, UNE: unilateral neck exploration, BNE: bilateral neck exploration, UNE > BNE: unilateral neck exploration followed by contralateral exploration if no enlarged parathyroid glands were identified on the first side, IS: imaging success, OT: operative time, OS: operative success, C: cost, HS: hospital stay, AE: adverse event, IL: incision length, P: pathology.
Source: Data from [13].

Table 20.4. Prospective multicenter study comparing five surgical regimens for primary hyperparathyroidism

Study population	Preoperative imaging	Intervention (number of available patients at follow-up)	Outcome hypercalcemia/ normocalcemia/ hypocalcemia (%)
325 patients undergoing initial Surgery for primary hyperparathyroidism due to solitary adenoma	not described.	1. Unilateral PTX after UNE (50)	2/96/2%
		2. Unilateral PTX after BNE (44)	3/90/7%
		3. BNE with removal of the enlarged gland and incisional biopsy of 1–2 normal-sized glands (84)	11/80/9%
		4. BNE with removal of the enlarged gland and incisional biopsy of 3 normal-sized glands (37)	3/92/5%
		5. BNE with removal of the enlarged gland but no biopsy (57)	0/98/2%

PTX: parathyroidectomy, UNE: unilateral neck exploration, BNE: bilateral neck exploration.
Source: Data from [23].

Table 20.5. Prospective, quasi-experimental studies of unilateral neck exploration

Author	Study population	Preoperative imaging	Intervention	Results
Russell [24]	90 PHPT	^{201}Tl-^{99m}Tc scan	Scan-directed UNE ($n = 48$) • Removal of adenoma and biopsy of the ipsilateral normal gland • Conversion to BNE if necessary BNE when the scan negative or UNE failed ($n = 42$) • Identification of all four parathyroids • Removal of obviously enlarged glands and biopsy of one normal-sized gland	UNE/BNE = 48/42 Cure rate 100% in the UNE patients at mean follow-up of 16.8 months ($n = 46$) Persistent hypercalcemia 14% who needed BNE (6/42)
Norman [17]	18 PHPT with a single adenoma	^{99m}Tc sestamibi scan	UNE • Removal and frozen section of an enlarged gland and search of a normal ipsilateral gland • Conversion to BNE if necessary	UNE/BNE = 18/0 Cure rate: 100% (18/18) at 6 months after surgery
Wei [21]	33 sporadic PHPT with a solitary adenoma	^{99m}Tc sestamibi scan	UNE followed by contralateral exploration • Removal of an enlarged gland and search and biopsy of a normal ipsilateral gland • Additional exploration and biopsy of contralateral glands	Cure rate: 100% (33/33) UNE would save approximately 30 min
Carty [26]	128 sporadic PHPT	Limited to high-risk patients in Strategy A; routine in Strategy B.	Strategy A ($n = 61$) • Palpation method for selective UNE • Conversion to BNE if necessary Strategy B ($n = 67$) • Routine use of both 99mTc sestamibi SPECT and ioPTH • Removal of an enlarged gland and search and biopsy of a normal ipsilateral gland • Conversion to BNE if necessary	Strategy A UNE/BNE = 25/36 Cure rate at 6 months: 95% (58/61) Strategy B UNE/BNE = 42/25 Cure rate at 6 months: 99% (66/67)
Moore [27]	48 sporadic PHPT	^{99m}Tc sestamibi scan, US if the scan failed.	UNE when the scan/US indicated a single disease, or both failed localization • Removal of adenoma and biopsy of an ipsilateral normal gland • Use of io-PTH • Use of a handheld scintillation detector when an adenoma could not be found on the predicted side • Conversion to BNE if necessary BNE when the scan indicated bilateral disease	UNE 32 (67%) UNE >> BNE 13 (27%) BNE 3 (6%) Cure rate 98% (47/48) at 3 months after surgery

PHPT: primary hyperparathyroidism, UNE: unilateral neck exploration, BNE: bilateral neck exploration, io-PTH: intraoperative PTH assay, US: ultrasonography.
Note: Studies with minimally invasive (focused) surgery were excluded.

et al. compared two surgical approaches to concise parathyroidectomy. Routine use of preoperative ^{99m}Tc sestamibi single photon emission computed tomography and intraoperative quick PTH measurement was associated with significant reductions in extent of surgery (i.e., more unilateral neck exploration) and the cure rate of 99% [26]. Moore and others examined the efficacy of unilateral neck exploration with the aid of preoperative localization modalities and intraoperative PTH measurements. Unilateral neck exploration was planned when the preoperative imaging studies indicated a single gland disease although bilateral search was made as needed. Thirty-two of the 48 patients (67%) had successful unilateral exploration while 16 patients ultimately underwent bilateral operation. Actual cure rate of this approach was 98% at 3 months after surgery [27]. These prospective studies suggested that unilateral neck exploration directed by preoperative localization techniques could be successful in around 60–70% of patients with seemingly sporadic primary hyperparathyroidism, and that cure rate can achieve over 95% given the contralateral side be explored if necessary and/or with the use of intraoperative quick PTH measurement.

Experimental Studies (Randomized Controlled Trials)

To date four randomized controlled trials comparing unilateral neck exploration with bilateral approach have been published; yet, it should be noted that the experiments differed in terms of study populations, interventions, and outcome measures [28–32]. (Table 20.6). In particular, three of them utilized focused removal of an

Table 20.6. Randomized controlled trial comparing unilateral (including focused parathyroidectomy) and bilateral neck explorations for primary hyperparathyroidism

	Study population	Intervention	Outcomes
Miccoli [28]	38 sporadic PHPT suitable for VAP (i.e., ultra-sonography indicates a solitary adenoma)	VAP group ($n = 20$) : • Focused removal of an adenoma • Use of io-PTH • Conversion to BNE if necessary BNE group ($n = 18$) : • Identify four glands • Removal and frozen section of an enlarged gland • No biopsy of normal sized gland • No io-PTH	Conversion to BNE in VAP group: 1/20 (5%) Cure rate: 19/19 (100%) in VAP group 17/17 (100%) in BNE group *1/20 (5%) in VAP group and 1/18 (6%) in BNE group were excluded from the analysis because they were found to have multi-glandular disease
Bergenfelz [29] Westerdahl [30]	91 sporadic PHPT	UNE group ($n = 47$): • Preoperative MIBI scan • Focused removal of an adenoma • Use of io-PTH • Conversion to BNE if UNE failed to make sure cure BNE group ($n = 44$): • No localization studies • Identify four glands • Removal and frozen section of an enlarged gland • No biopsy of normal sized gland • No io-PTH	Conversion to BNE in the UNE group: 18/47 (38%) Cure rate at 6 weeks after surgery: 45/47 (96%) in UNE group 43/44 (98%) in BNE group Recurrence rate at 5 years after surgery: 2/38 (5%) in UNE group 1/33 (3%) in BNE group Overall 6 patients have found to have persistent (3) or recurrent (3) primary hyperparathyroidism. Three of the 6 patients have found to have multiple endocrine neoplasia mutations

Table 20.6. (continued)

	Study population	Intervention	Outcomes
Bergenfelz [31]	50 PHPT with a solitary adenoma localized by ^{99m}Tc sestamibi scan.	MIP ($n = 25$) • Targeted resection of adenoma • Io-PTH • Frozen-section analysis • Local anesthesia • Conversion to BNE if necessary BNE ($n = 25$) • Identify all four parathyroid glands • Excision of enlarged glands • Frozen-section analysis • No io-PTH • General anesthesia	Conversion to BNE in the MIP group: 3/25 (12%) Cure rate at 1 and 6 months MIP: 24/25 BNE: 25/25
Russell [32]	100 PHPT whose single tumor was identified at operation at the site suggested by the preoperative dual-isotope subtraction scanning using ^{99m}Tc and Tc-labeled sestamibi	Scan-directed UNE ($n = 54$) • Removal of adenoma and identification of the ipsilateral normal gland • No io-PTH BNE ($n = 46$) • Identify the two parathyroids on the contra-lateral side • Removal of obviously enlarged glands • No io-PTH	Cure rate at a mean of 23 months' follow-up. UNE: 54/54 BNE: 46/46

PHPT: primary hyperparathyroidism,
VAP: video-assisted parathyroidectomy,
MIP: minimally invasive parathyroidectomy,
BNE: bilateral neck exploration,
UNE: unilateral neck exploration,
io-PTH: intraoperative quick PTH measurement.

adenoma rather than total unilateral exploration. Miccoli et al. compared video-assisted parathyroidectomy (VAP) against conventional bilateral neck exploration (bilateral neck exploration) with a study population consisting of 38 patients with sporadic primary hyperparathyroidism *suitable for VAP* (i.e., ultrasonography indicated a solitary parathyroid adenoma). Cure rates were 100% in both groups while the VAP group experienced less costs, shorter operative times, less pain, and better cosmetic results than the bilateral neck exploration group [28]. Bergenfelz and others allocated either unilateral neck exploration or bilateral neck exploration to 91 patients with seemingly sporadic primary hyperparathyroidism. Patients in the unilateral neck-exploration group underwent both preoperative ^{99m}Tc sestamibi scan and intraoperative monitoring of serum PTH whereas those in the bilateral neck-exploration group had neither localization studies nor intraoperative PTH measurement. In the unilateral group, no attempts were made to visualize normal

parathyroid glands. Cure rates, operative time, cost, and postoperative pain were similar between the two groups [29]. Results of 5-year follow-up of the trial have recently been reported by Westerdahl and Bergenfelz. In addition to three persistent cases, three patients experienced disease recurrence, two in the unilateral neck exploration group, and one in the bilateral neck exploration group on the intention-to-treat analysis despite the fact that five of them actually underwent bilateral neck exploration [30]. A trial in Germany randomized 50 patients with primary hyperparathyroidism with a solitary adenoma demonstrated by sestamibi scintigraphy to either MIP under local anesthesia or bilateral neck exploration under general anesthesia. Cure rates by the primary surgery were 96% in the MIP group and 100% in the bilateral exploration group, respectively [31]. Russell et al. compared scan-directed unilateral neck exploration with bilateral one. In this trial, 100 patients were randomized to one of the interventions during the surgery if a single adenoma was identified at the site suggested by the preoperative scintigraphy. All patients were cured in both groups [32]. Noninferiority, or even advantages, of unilateral neck exploration or focused parathyroidectomy have been demonstrated through these randomized controlled trials.

Bilateral Versus Unilateral Neck Exploration: In Practice

Evidence demonstrated that unilateral neck exploration or focused surgery with adequate preoperative imaging procedures and intraoperative quick PTH measurement have, *on average*, equivalent cure rate and even less invasive when compared with the use of bilateral neck exploration in treating primary hyperparathyroidism. *On an individual basis*, however, selecting a particular surgical approach depends on various factors. In addition to the expertise of surgeons and the validity of preoperative localization studies available, the success of the limited approach is highly dependent on the possibility of multiple gland disease of the individual [33].

Possibility of Multiglandular Disease – Prevalence

The prevalence of multiglandular disease in primary hyperparathyroidism had been estimated to be around 15% [29]. In 1996, Moliani et al. found the figure to be 5% in their prospective study where 110 patients with seemingly sporadic primary hyperparathyroidism underwent focused parathyroidectomy using quick intraoperative PTH measurement [34]. Lee and Norton reviewed their 214 consecutive patients who underwent bilateral neck exploration and found that 44 (20.6%) had multiglandular disease, although they did not indicate whether they excluded patients with multiple endocrine neoplasia from the study population [35]. In the same article, the authors conducted a literature review to determine the prevalence of single adenoma and multiglandular disease in published studies of unilateral and bilateral neck exploration for primary hyperparathyroidism. Retrieved articles were grouped according to operative technique irrespective of study design and study population. Of 2,166 patients in 14 studies who underwent bilateral neck exploration, 19.3% had multiglandular disease, whereas the prevalence was found to be 5.3% among 2,095 patients from 31 published reports adopting a *focused* unilateral approach [35]. As the authors cited, the observed difference in the prevalence can be explained in some ways. First, selection bias may play a role in assembling study populations. Patients whose preoperative localization studies indicated multiglandular disease were less likely to be candidates for unilateral or even focused operations. Second, the definition of multiglandular disease could be different among selected studies, namely *functional* versus *morphological* [29]. Thus studies with unilateral exploration might underestimate the prevalence while those with bilateral approach might overestimate the figure. Prevalence data of multiglandular disease from four prospective studies and four randomized trials cited in the previous sections were summarized in Table 20.7. Although exact histopathological diagnoses of multiglandular disease were not described in three randomized trials, the overall prevalence ranged from 0 to 15%. It should be noted that the confidence intervals

Table 20.7. Prevalence of multiglandular disease observed in prospective studies

Author	Study design	Definition of multiple gland disease	Prevalence of multiple gland disease
Russel [24]	Prospective, quasi-experimental	Not described	Hyperplasia 7% (3/42 underwent BNE)
Wei [21]	Prospective, quasi-experimental	Not described	0% (0/33 underwent BNE)
Carty [26]	Prospective, quasi-experimental	Not described.	Hyperplasia 9% (11/128) Double adenomas 4% (5/128)
Moore [27]	Prospective, quasi-experimental	Not described.	Hyperplasia 2% (1/48) Double adenomas 13% (6/48)
Miccoli [28]	Randomized controlled trial	Morphological (BNE) and functional (VAP)	5% (1/20) in VAP group 6% (1/18) in BNE group Overall 5% (2/38).
Bergenfelz [29] Westerdahl [30]	Randomized controlled trial	UNE group: functional and histopathology BNE group: histopathology	13% (6/47) in UNE group 11% (5/44) in BNE group Overall 12% (11/91)
Bergenfelz [31]	Randomized controlled trial	MIP group: functional and histopathology BNE group: histopathology	4% (1/25) in MIP group 8% (2/25) in BNE group Overall 6% (3/50).
Russell [32]	Randomized controlled trial	Histological	0% (0/54) in UNE group 7% (3/46) in BNE group (Double adenomas) Overall 3% (3/100)

VAP: video-assisted parathyroidectomy, MIP: minimally invasive parathyroidectomy, BNE: bilateral neck exploration, UNE: unilateral neck exploration, io-PTH: intraoperative quick PTH measurement.

of the figures should be fairly large because the numbers of patients in each study were relatively small.

Possibility of Multiglandular Disease – Clinical Characteristics

One of the important clinicians' jobs is to characterize a patient so that tests and interventions can fit her or his best outcomes. In fact, the ultimate goal of clinical epidemiology is to contribute this through thoughtful use of available *evidence*. Kebebew et al. developed a scoring model with data of preoperative clinical, biochemical, and imaging studies to differentiate patients with single from multiple gland disease by reviewing medical record of 238 consecutive patients with primary hyperparathyroidism including multiple endocrine neoplasia as well as persistent or recurrent diseases [36]. Their CaPTHUS dichotomous scoring model consisted of five variables: (1) preoperative total calcium level $\geq$3 mmol/l ($\geq$12 mg/dl); (2) intact PTH level $\geq$2 times the upper limit of normal PTH levels; (3) sestamibi scan results positive for one enlarged parathyroid gland; (4) neck ultrasound results positive for one enlarged parathyroid gland; and (5) concordant sestamibi and neck ultrasound study results (identifying one enlarged gland on the same side of the neck). A total score of 3 or greater had a sensitivity of 44% and specificity of 100% in predicting single-gland disease. Since there were no false positives, the authors concluded that patients with a score of 3 or higher could undergo an MIP without the routine use of intraoperative PTH or additional imaging studies. The model, however, remains to be validated because it was derived from a retrospective analysis. In fact, even before developing the model, the authors were successful in curing 99.2% of their patients in which 65% underwent unilateral or focused neck

Table 20.8. Conditions when bilateral neck exploration needs to be considered

Family history	√ Primary hyperparathyroidism
	√ Urolithiasis
	√ Multiple endocrine neoplasia
Biochemical data	√ Mild hypercalcemia
	√ Mild elevation of PTH
Localization studies	√ Negative
	√ Equivocal
	√ Suggesting multiple gland disease
	√ Discordant results among several studies
Intraoperative findings at UNE	√ No adenoma
	√ Two enlarged glands

UNE: unilateral neck exploration.

explorations. Although such a quantitative model can be useful, it may be more practical to consider each characteristic associated with multiglandular disease in individualizing the decision as to whether the neck should be explored bilaterally or not (Table 20.8).

Conclusions

There is no doubt that bilateral neck exploration has been the gold standard as the surgical procedure for primary hyperparathyroidism [37]. With the advent of modern medical technologies, however, limited or focused approaches have become suitable alternatives for *selected* patients as the history has witnessed. An endocrine surgeon should use her or his expertise with deep understandings of the disease so that best outcomes are available for *each* patient.

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21

Reoperative Parathyroid Surgery

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Every surgeon must learn to come to terms with the inadequacies and sometimes downright failures of his or her actions that will be inevitable companions during a surgical life [1].

Introduction

An operation for primary hyperparathyroidism (PHPT) will result in restoration of normocalcemia in 95–98% of patients when performed by an experienced surgeon [2–6]. Patients to be considered candidates for reoperative parathyroid surgery are those in whom previous operation(s) have failed to achieve lasting cure of their hypercalcaemia. These patients have either persistent or recurrent hyperparathyroidism (HPT).

History

In 1925, the year that Felix Mandl performed the first successful operation for hyperparathyroidism in a patient with von Recklinghausen's disease [7], Oscar Hirsch, a Viennese surgeon failed to identify a parathyroid tumor in the neck of another patient with von Recklinghausen's disease. In 1926, Edward Richardson in Boston, performed two operations on Charles Martell, a sea captain with hyperparathyroidism, but could not find an abnormal parathyroid gland. Martell eventually had seven operations before his parathyroid tumour was found in the mediastinum and removed.

Felix Mandl in July 1926 removed an abnormal parathyroid gland from the neck of Herr Albert who had a high blood and urinary calcium with 'apparently good outcome'. Six years later Albert's disease returned and at reoperation, Mandl failed to identify any abnormal parathyroid tissue, the patient died from renal failure [8]. In 1931, Sir James Walton reported the first series of parathyroid operations performed in Britain; he had to reoperate on the fourth patient to find a mediastinal adenoma which he removed via the neck.

Definition

Persistent hyperparathyroidism is hypercalcemia that remains after neck exploration or recurs within 6 months of initial parathyroid surgery [9, 10]. Patients with persistent disease may have transient postoperative normocalcemia and a subsequent elevation, or serum calcium levels that remain high following surgery.

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Recurrent HPT occurs more than 6 months after initial successful parathyroidectomy with postoperative normocalcemia.

The Extent of the Problem

Persistent or recurrent hyperparathyroidism for PHPT occurs in expert hands after 2–5% of initial procedures [11]. Persistent HPT is associated with single- or multiglandular disease, whereas recurrent HPT usually results from multiglandular disease [9, 12]. The incidence of recurrent HPT is higher in patients with multiple endocrine neoplasia (MEN) compared with sporadic HPT, reported in 20–30% of patients with MEN I and II after subtotal parathyroidectomy with higher rates observed in patients having less than four gland parathyroid resections [13–15]. In renal HPT (RHPT), the incidence of recurrent or persistent HPT after subtotal parathyroidectomy is reported as 2–15% [16–18]. The incidence of recurrent HPT arising from autografted parathyroid tissue in RHPT is 3–16% [19–22].

The gold standard for the treatment of hyperparathyroidism has been bilateral neck exploration. Today, surgeons may perform less than four gland exploration, i.e., scan-directed unilateral neck exploration, a focused small incision approach, or a minimally invasive videoscopic parathyroidectomy [23–27]. Initial concerns that less than four gland exploration may render patients more vulnerable to persistent/recurrent HPT [28, 29] have not been substantiated [25, 30–35]. The results of a 5-year follow-up of 91 patients with PHPT randomized to unilateral or bilateral neck exploration showed that four patients in the unilateral group, and two patients in the bilateral group, were found to have persistent/recurrent disease. Half of all the patients with persistent/recurrent disease in this study were unexpectedly found to have germ line mutations associated with MEN [36]. Whether a less than four gland neck exploration/unilateral approach underestimate the incidence of multiglandular disease, time will tell [37].

Why Does an Initial Operation Fail? (Table 21.1)

The serum calcium remains high after an initial parathyroid operation because of:

1. Incorrect diagnosis, i.e., not HPT.
2. The surgeon calls an abnormal parathyroid gland ‘normal’, i.e., misinterpretation.
3. Failure to recognize the presence of multiglandular disease (PHPT, RHPT, familial disease).
4. Limitation of the surgical approach – unilateral neck exploration with contralateral pathology or a focused approach in which the pathology is in the non ‘explored’ ipsilateral gland).
5. The surgeon cannot find the abnormal gland/s (retained pathology) due to unrecognized eutopic, ectopic, or supernumerary gland.
6. Rare pathology – incomplete resection of parathyroid carcinoma or parathyromatosis.

Alternatively, the failure to cure at initial operation can be summarized in relation to the surgical approach:

A. Patient had a unilateral neck exploration for PHPT and abnormal parathyroid tissue was not identified.

Table 21.1. Causes of failure of initial operation for PHPT

Unrecognized pathology	Incorrect diagnosis	Incomplete resection
1. Eutopic abnormal gland(s) 2. Unrecognized multiglandular disease, e.g., adenoma, hyperplasia-sporadic or familial (MEN or non-MEN), renal hyperparathyroidism 3. Ectopic abnormal gland 4. Supernumerary glands	High calcium, high PTH 1. FHH 2. Ectopic PTH production High calcium, low PTH 1. Malignancy (PTHrP) and/or bone metastasis 2. Other causes of hypercalcemia	1. Incomplete excision of multiglandular disease, i.e., remnant size 2. Parathyroid cancer

The surgeon found:

i) Two normal glands. The likely cause of failure is one or more diseased parathyroid glands on the contralateral side, or supernumerary glands.
ii) One normal gland. The cause of failure is a missing abnormal gland in either a normal anatomic location but the surgeon could not find it, or the abnormal gland is in an ectopic location.
iii) No parathyroid glands identified. The surgeon is either inexperienced or the glands are in ectopic locations.

B. Focused approach uniglandular exploration. The surgeon found:

i) No parathyroid gland. This is due to inexperience on the part of the surgeon, or incorrect preoperative localization or, an unidentified ectopic gland, e.g., intrathyroidal (Fig. 21.1).
ii) A single abnormal gland. The cause of failure is multiglandular disease. The proportion of surgeons who routinely look for a second gland during a focused approach parathyroidectomy is unknown.

C. Bilateral neck exploration
Failure to cure is explained by:

i) The surgeon not identifying one or more abnormal parathyroid glands (which may be eutopic, ectopic, or supernumerary in location) or
ii) Finding four normal parathyroid glands in which case the cause is a supernumerary gland or
iii) The surgeon has incorrectly evaluated identified parathyroid tissue.

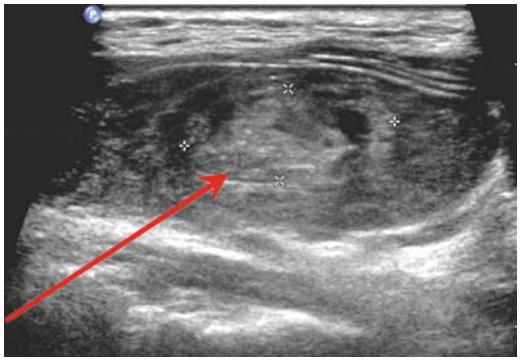

Fig. 21.1. Intrathyroidal parathyroid. This patient's USS, MIBI, and CT were negative after failed initial exploration. USS had showed a thyroid nodule (above) with follicular cytology. At reexploration the right inferior gland was missing and a thyroid lobectomy showed an intrathyroidal parathyroid gland cured the patients' persistent hyperparathyroidism. (Courtesy of Dr. Catherine Clout, Consultant Radiologist, Northern General Hospital, Sheffield).

Reasons for Failure

1. *Eutopic abnormal gland (single gland disease)*: The abnormal gland is in a normal anatomic location but the surgeon failed to identify it. In up to 79% of patients with recurrent/ persistent HPT, the missed abnormal gland will be found in a normal anatomic location. Superior parathyroid glands are more symmetrical in position than the inferior glands [38], usually found above the inferior thyroid artery, posterior to the recurrent laryngeal nerve (RLN). The inferior parathyroid glands are anterior to the RLN and below the inferior thyroid artery. For anatomical locations of normal glands, see Chapter 15.

2. *Ectopic abnormal gland*: If fewer than four normal parathyroid glands were found at an initial bilateral operation, then failure may be due to an abnormal gland in an ectopic location [39, 40]. Up to 25% of abnormal parathyroid glands are located in ectopic sites variously positioned in the neck or superior mediastinum. Failure of descent from the third pharyngeal pouch during embryological development can result in the inferior parathyroid gland remaining high in the neck above the upper thyroid pole and medial to the carotid sheath, or low within the thymus [38]. The most common site for ectopic inferior glands is within the body of the thymus.

Ectopic superior parathyroid glands can be found in para-esophageal locations in the neck/posterior superior mediastinum. Other rare sites of ectopic parathyroid tissue include the carotid sheath, thyroid gland, vagus nerve sheath, posterior to the innominate vein, aortopulmonary window, and the pericardium [39–41] (Table 21.2).

3. *Eutopic abnormal gland (multiple)*: Abnormal parathyroid tissue may be left behind at initial operation due to the presence of unrecognized multiglandular disease. This can be multiple adenoma [33] or hyperplasia of parathyroid glands. In PHPT, 87–90%

Table 21.2. Ectopic glands identified at reoperative parathyroid surgery [38]

	Intrathymic (%)	Antero superior mediastinal (%)	Intrathyroidal (%)	Thyro-thymic ligament (%)	Submandibular (%)	Tracheooesophageal groove (%)	Retro-oesophageal (%)	Postero-superior mediastinal. (%)	Carotid sheath (%)	Para-oesophageal (%)
Ectopic inferior glands (62%)	30	22	22	17	17	–	–	–	–	–
Ectopic superior glands (38%)	–	–	7	–	–	43	22	14	7	7

Source: Data from [41].

patients have a single adenoma, 9% have multiglandular hyperplasia, and 5–10% have multiple adenomas [42–44]. In familial HPT and RHPT, multigland disease is more common but the gland enlargement may be asymmetrical at the time of initial surgery. Multiglandular disease has been found in 90 and 83% of patients with MEN 1 and MEN 2, respectively [45].

4. *Supernumerary gland*: In 5% of patients who undergo surgery for PHPT it is possible to find a supernumerary gland as the cause [35–37]. In an autopsy series of 503 cases, 84% had four glands, 3% had three glands, and supernumerary glands were found in 13%, most frequently a fifth gland in the thymus [38]. In patients with end-stage renal failure who undergo surgery, the incidence of supernumerary glands is reported as high as 16.5–30%, over 60% of which are located in the thymus and these are the cause of persistent/recurrent disease when not removed at initial exploration [39, 46, 47]. In MEN, supernumerary glands occur in 20–30%, of patients, mostly in the thymus and should be looked for to avoid high rates of recurrent HPT [48].

5. *Incomplete resection of lesion*: If at an initial operation in patients with multiglandular disease, resection of abnormal parathyroid tissue was inadequate, i.e., less than a subtotal parathyroidectomy or too large a remnant of parathyroid tissue was left behind in the neck, persistent HPT will result [49, 50].

Recurrent HPT in such patients occurs when there is regrowth of remnant parathyroid tissue or hyperfunction of parathyroid rests in the neck or, the autograft (after total parathyroidectomy). The stimulus that resulted in the development of initial HPT causes hyperfunction of any remnant parathyroid tissue [51].

Incomplete excision of parathyroid carcinoma at initial surgery due to locally advanced disease or nodal/systemic metastasis present at the time of surgery can result in recurrent or persistent HPT [35–37].

Parathyromatosis is a rare condition in which multiple nodules of hyperfunctioning parathyroid tissue are scattered through the neck and mediastinum due to spillage of parathyroid tissue at first time surgery, usually in renal patients. The growth of hyperfunctioning parathyroid tissue results in recurrent HPT [52–58].

6. *Incorrect diagnosis-persistent hypercalcaemia not caused by PHPT*: Failure to cure hypercalcemia at initial operation is inevitable if the diagnosis of PHPT was incorrect. Patients with hypercalcemia from causes such as familial hypocalciuric hypercalcemia (FHH), malignancy, and para-neoplastic syndromes will not be cured by parathyroidectomy.

Care of the Patient with Failed Initial Surgery

In the immediate postoperative phase the patient should be informed of the outcome of the initial exploration and the care pathway that may follow. Significant hypercalcemia requires monitoring and sometimes medical treatment to include adequate hydration and drug treatment, e.g., biphosphonates, calcimimetics therapy [59]. There should be a follow-up plan for regular measurement and review of the serum calcium after discharge from hospital whilst the patient awaits further investigations and treatment.

Patients should be referred to an endocrine surgical team with experience of reoperative parathyroid surgery.

At the referral center, clinical management is based on the outcome of the following enquiries (Fig. 21.2):

1. *Symptoms and severity of hypercalcaemia*: History of symptoms and complications of hypercalcemia should be noted, e.g., fractures, nephrolithiasis, and calciphylaxis.
2. *Family history of HPT*: A detailed history should be taken to identify affected family members with hypercalcaemia and other associated conditions which may suggest familial disease (MEN1/2 or non MEN familial HPT).
3. *Confirmation of the biochemical diagnosis of HPT*: The results of investigations including adjusted calcium, parathyroid hormone (PTH), urea and electrolytes, creatinine, 24 hour urinary calcium, and vitamin D should be reviewed. Patients with vitamin D deficiency and FHH as a cause of hypercalcemia should be excluded prior to further investigations.
4. *Localization studies/operation findings and pathology*: The results of localization studies performed prior to the initial exploration should be reviewed and correlated with operative and pathology findings.

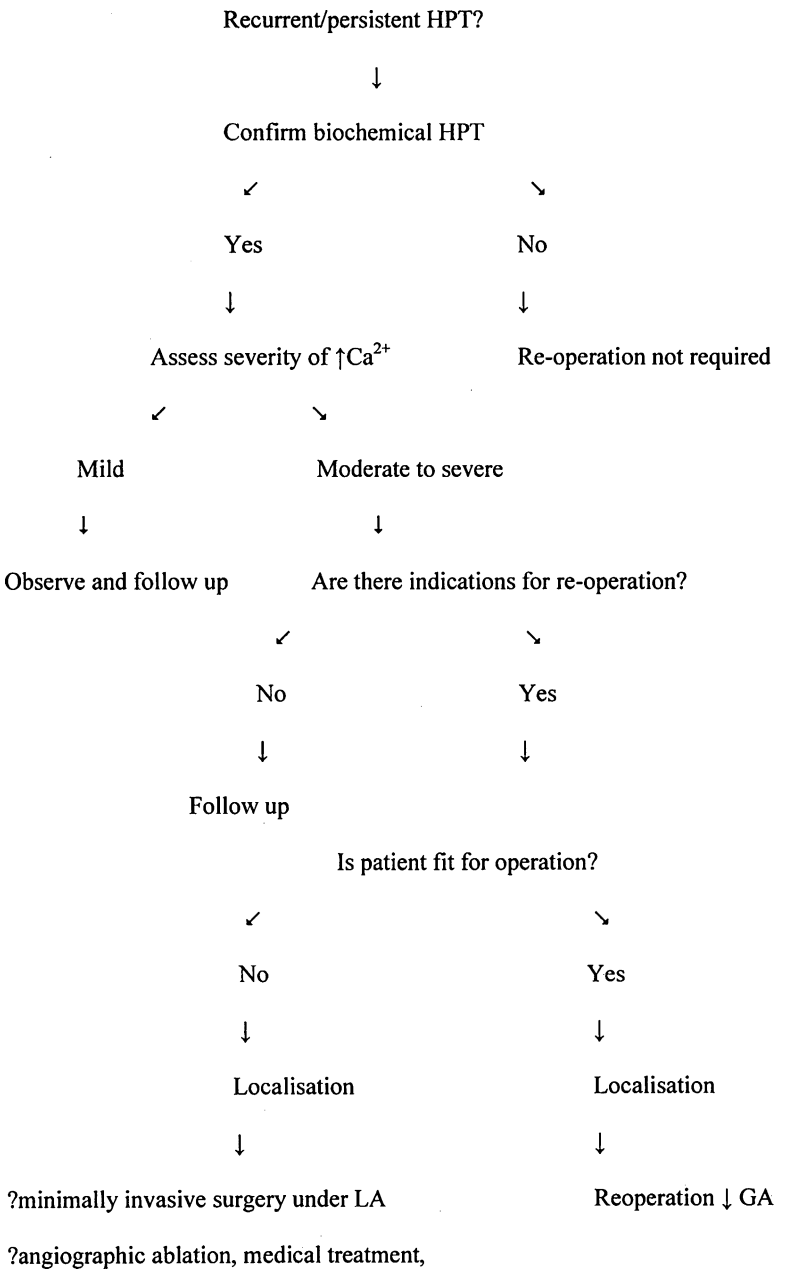

Fig. 21.2. Flow chart.

The key to success in reoperative parathyroid surgery is a clear understanding of the findings and procedure carried out at the initial operation. What the surgeon found and which parathyroid glands were identified and removed should be clarified, in addition to the areas which were and were not explored. It is important to know if transcervical thymectomy was performed and if any parathyroid tissue was found within it. All this information serves as a road map for reoperation.

An experienced pathologist should review specimens from the initial exploration to confirm the presence (or absence) of parathyroid tissue and the pathological features which might suggest single or multiglandular disease.

5. *An assessment of HPT-related comorbidity*: If available, the results of prior bone mineral density (DEXA) scans (T scores) should be reviewed to identify patients with significant osteoporosis in whom reoperation may be beneficial. Ultrasound (USS) of the kidneys may identify calculus disease.
6. *Assessment of vocal cord mobility*: All patients considered for reoperation should undergo laryngoscopy. The need for reoperation in a patient with unilateral RLN palsy should be carefully considered; the potential risk of injury to the contralateral nerve in a patient with a damaged nerve from the initial operation should be weighed against the benefits of exploration of that side.
7. Are there indications for reoperation?

The indications for reoperation include one or more of the following:

- Symptomatic hypercalcemia.
- Severe hypercalcemia (>3.0 mmol/l).
- Hypercalcemia with complications such as renal stones, calciphylaxis, pancreatitis, osteoporosis, fractures, etc.
- In renal patients, high PTH, calcium phosphate product, high alkaline phosphatase, and/or symptoms/complications, e.g., calciphylaxis.
- Young patients with mild to moderate hypercalcemia.

Parathyroid Gland Localization in Recurrent/Persistent HPT

When there is a clear indication/s for reoperation, parathyroid localization studies should be requested. A repeat of investigations carried out prior to the initial operation may be necessary, as well as additional tests to confirm the location/s of abnormal parathyroid gland/s. Remember that localization studies are less reliable when there is multiglandular involvement as they may fail to identify all enlarged glands.

Preoperative

1. *Ultrasound*: USS in recurrent/persistent HPT requires a radiologist with interest and experience in parathyroid imaging to whom information about the operative findings and areas in the neck which have been explored at initial surgery are important guides. Neck USS immediately after a failed initial exploration may not be comfortable for the patient but can usually be performed after the first week [60].

Postoperative tissue reaction may obscure normal tissue planes and vascularity which are essential for the identification of abnormal parathyroid glands. The sensitivity of USS in persistent/recurrent HPT is 50–87%, with a positive predictive value of up to 84%, and a false-negative rate close to 11% [61–67].

USS-guided fine-needle aspiration and measurement of PTH from suspected parathyroid lesions has been found to have 100% specificity and allows a directed surgical resection avoiding further invasive work up when the aspirate is positive [67–75].

2. *MIBI scan*: The sensitivity of MIBI in persistent/recurrent HPT is 50–82% [62, 63, 76–79].

The combination of ultrasonography and sestamibi scan gives sensitivity rates ranging between 64–90% and a true-positive rate of over 90% with few false positives. Reoperation can proceed if these results are positive and concordant [60, 80, 81] (Fig. 21.3).

3. *Computerized tomography (CT) scanning and fusion imaging*: The sensitivity of CT in persistent/recurrent disease is 67–86% but the false-positive result rate is high at 14% [63, 82, 83]. CT with contrast after neck operations may be difficult to interpret because of scar tissue and artifacts and should be reserved for patients in whom a mediastinal gland is suspected, especially when USS and MIBI scans are negative [83, 84].

SPECT can be combined with MIBI to produce fusion images, and this increases the sensitivity of the procedure to 91% and provides better anatomical location which is helpful for the surgeon [85–87] (Fig. 21.4).

4. *Magnetic resonance imaging (MRI)*: Enlarged parathyroid glands have increased intensity on T2-weighted images on MRI. The sensitivity of MRI in reoperative parathyroid surgery is 64–88% with a positive predictive

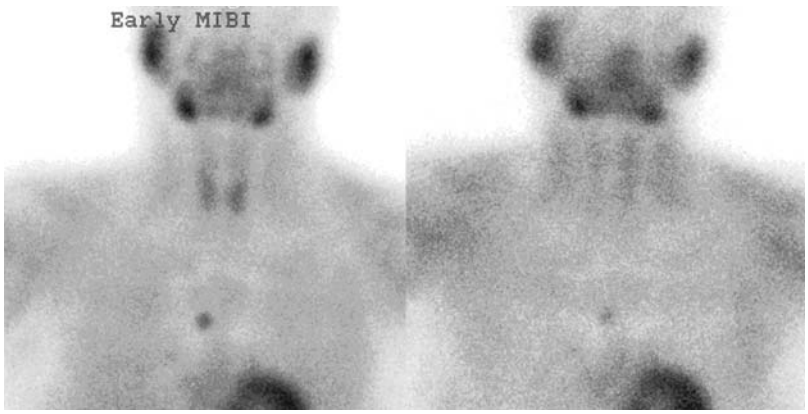

Fig. 21.3. A mediastinal abnormal parathyroid gland identified on MIBI in a patient with four normal cervical glands. This supernumerary gland was removed at reoperation from the anterior mediastinum.

value of 89% [88, 89], 10% better than for CT, in addition to lower false-positive rates/higher true-positive rates. MRI however cannot be performed in claustrophobic patients, or those with metallic heart implants. It cannot be used to guide FNA of suspected parathyroid lesions for PTH assay.

5. *Positron emission tomography (PET)*: A positron emitting analogue of ((d))-glucose, 2-(fluorine-18-fluoro-2-deoxy-((d))-glucose (FDG), allows glucose metabolism to be measured and evaluated using PET. There is differential concentration of FDG in abnormal parathyroid tissue compared with normal glands and the sensitivity in recurrent and persistent HPT is up to 79–90% [67, 90, 91]. FDG may also be taken up by thyroid tissue in thyroiditis, thyroid adenoma, and carcinoma, as well as other malignant tissues in the neck or superior mediastinum. It may be useful if parathyroid localization using the above-mentioned modalities is negative (Fig. 21.5), but the initial reports of promising results with PET have not translated into major impact on clinical practice.

6. *Selective venous sampling (SVS) and angiography*: SVS for PTH is indicated when noninvasive tests are negative, equivocal, or inconclusive. A catheter is inserted into the femoral vein and guided to cervical or mediastinal veins and their branches under X-ray control to obtain blood samples for PTH. Values of PTH in the cervical or mediastinal vein samples are compared with those in peripheral venous blood to provide a combined anatomical/biochemical gradient of PTH concentrations. A greater than 1.5- to 2-fold increase in PTH levels is viewed as a positive result, which in practical terms allows regionalization of the missing gland into right

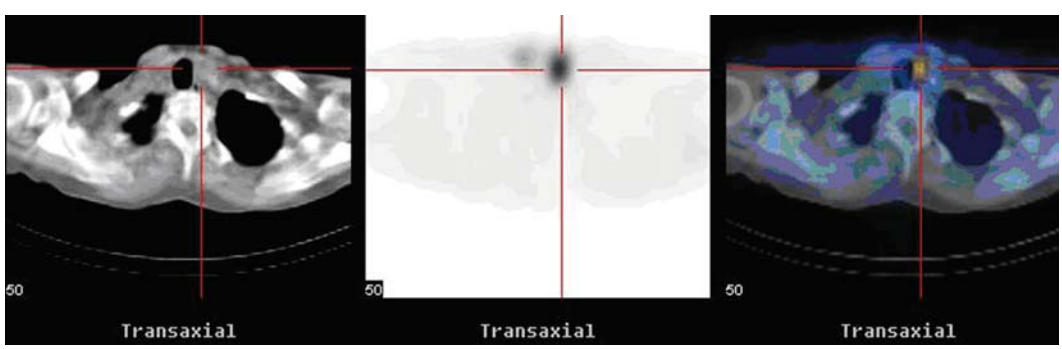

Fig. 21.4. MIBI/CT fusion image of a parathyroid adenoma medial to the left thyroid lobe.

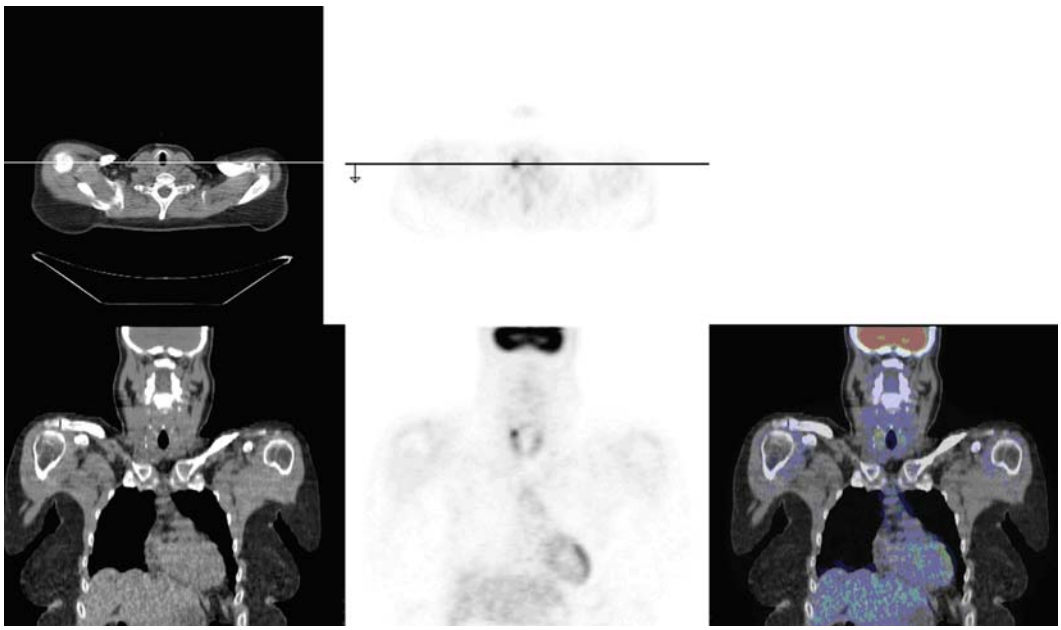

Fig. 21.5. PET/CT fusion image of right superior parathyroid.

cervical, left cervical, or thymic/mediastinal region [84]. SVS is useful in identification of mediastinal and cervical pathology. The technique can be highly sensitive (up to 94%) [64, 65] but without concomitant angiography has a false-positive rate of 6–18% [67, 92, 93].

Selective angiography should be considered at the time of SVS to examine branches of the external carotids, the internal mammary arteries, and the thyrocervical trunks in order to identify the characteristic contrast 'vascular blush' (Fig. 21.6). Sensitivity of the technique approaches 60%, when combined with SVS this increases to 91–95% [94]. In our center, from 1999 to 2007, we performed SVS for recurrent/persistent PHPT in 13 patients. SVS correctly identified the abnormal parathyroid gland in 12 cases (sensitivity of 92%). Simultaneous selective angiography was performed in six cases but revealed an abnormality concordant with venous sampling in only two cases.

7. *Casanova test*: This test is used to distinguish neck recurrence (supernumerary gland) from hyperfunctioning forearm parathyroid autograft after total parathyroidectomy with parathyroid autotransplantation. Patients with a hyperfunctioning forearm autograft will demonstrate a significant reduction in PTH following induced

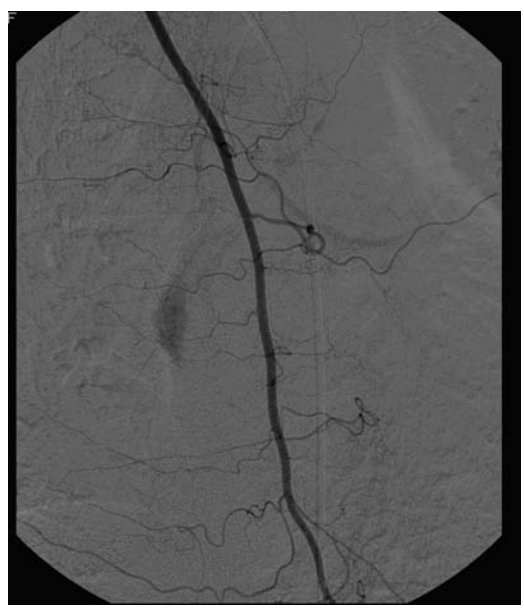

Fig. 21.6. Internal mammary angiogram showing a hypervascular lesion in the right side of the mediastinum near the right atrium (vascular blush of parathyroid adenoma) – a parathyroid adenoma. Other localization tests prior to reoperation including SVS did not localize this lesion. (Courtesy of Professor Peter Gaines, Consultant Radiologist, Northern General Hospital, Sheffield).

ischemia in the graft-bearing arm compared with the nongraft-bearing arm [95, 96].

Intraoperative Localization

1. *Methylene blue*: Abnormal parathyroid glands take up blue stain when a preoperative infusion of methylene blue (5 mg/kg in 5% Dextrose) is given one hour before surgery [97]. However recent reports because reports suggest that methylene blue can precipitate serotonin toxicity in patients taking selective serotonin uptake inhibitors [98] and cause temporary adverse effects on the central nervous system.

2. *Intraoperative MIBI*: Intraoperative sestamibi scanning in reoperative surgery is reported better than preoperative scanning with sensitivity of up to 91% [99, 100].

3. *Intraoperative bilateral jugular vein sampling for PTH*: Venous sampling from both internal jugular veins for PTH at the start of an exploration is particularly useful when localization studies have not shown any abnormality [101]. Differential elevation of the PTH level will indicate the side of the neck where hyperfunctioning parathyroid gland is likely to be found, this side should be explored first.

Generally, localization studies should begin with USS and MIBI, if these are negative or nonconcordant; selection of further tests as mentioned above will be directed by the suspected location of the abnormal parathyroid gland/s. Invasive tests should be performed selectively, when noninvasive test is negative.

Reoperative Surgery

Reoperation should be exclusively performed by an experienced endocrine surgeon, and frozen section pathology, reporting to confirm parathyroid tissue, and intraoperative PTH assay, to confirm biochemical cure, should be available [102].

In ideal circumstances localization studies will have provided sufficient information to guide a planned unilateral/bilateral cervical or mediastinal exploration. There are however cases when localization test is negative and bilateral cervical exploration is therefore mandatory.

The surgeon should obtain informed consent from the patient regarding the proposed intervention, taking time to reexplain the indications and implications of reoperative surgery, including the details of risks and complications (bleeding, temporary or permanent damage to the RLN/s with risk of tracheostomy, failure to achieve cure, and hypoparathyroidism).

Adequate planning should include allowance for prolonged operating time, and if required, the availability of a surgeon to assist with sternotomy.

Operative Strategy

The strategy in reoperative PHPT is as follows:

a) Perform localization directed cervical and/or mediastinal exploration.
b) Excise abnormal parathyroid gland/s.
c) Perform additional procedures such as thymectomy in patients with multiglandular disease and or autotransplantation or cryopreservation of parathyroid tissue in RHPT/MEN.
d) Confirm successful identification of parathyroid tissue with frozen section and confirm biochemical cure with intraoperative PTH.
e) Minimize operative complications such as damage to recurrent the laryngeal nerve/s and hypoparathyroidism.

Positive Localization

The operative strategy will of course be influenced by the surgical and pathological findings at initial surgery as well as the results of subsequent localization studies. When the latter have identified the 'expected' abnormal parathyroid gland/s as

1. *Single gland disease*: Unilateral neck exploration is the operation of choice [103]. The techniques of first time unilateral neck exploration can be equally applied to reoperative parathyroid surgery. A lateral incision or conventional cervicotomy skin incision can be used. A lateral approach obviates the need for dissection through midline scar tissue, the plane between the medial border of the sternomastoid muscle at the level of the thyroid gland and the lateral border of the

strap muscles is developed. The strap muscles and thyroid gland are retracted medially and the plane deepened until one can see and palpate the vertebral column posteriorly and the esophagus medially. The inferior thyroid artery and RLN should be identified. This procedure can be carried out under local or general anesthesia.

2. *Multiglandular disease*: When preoperative localization studies are positive for multiglandular disease or multiglandular enlargement is suspected – hyperplasia was identified on histology from tissue excised at a previous operation; assessment of all residual parathyroid tissue is required. A systematic approach should be used to guide the surgeon to the parathyroid glands [104]. The surgical options include excision of abnormal gland/s in case of multiple adenomas, and subtotal parathyroidectomy or total parathyroidectomy with or without autotransplantation when the diagnosis is hyperplasia/MEN.

In patients with multiglandular disease, cervical thymectomy should be carried out in addition to parathyroidectomy.

3. *Mediastinal parathyroid gland*: Mediastinal exploration should only be performed when there is evidence from localization studies that the hyperfunctioning gland is in the mediastinum. In our center, mediastinal exploration is not undertaken without positive preoperative localization.

The mediastinum can be explored via a partial or complete sternotomy, or a thoracoscopic approach can be employed if available, appropriate, and feasible. Mediastinal parathyroids that are located at the level of the innominate vein in the anterior superior mediastinum may be retrievable via a cervical approach, but if necessary can be removed using a partial sternotomy. Parathyroid glands that are low in the anterior mediastinum or in the middle mediastinum require a complete sternotomy. The potential complications and morbidity associated with open sternotomy may be reduced by the thoracoscopic approach, but this has not been widely accepted as standard treatment [105–110]. The UK National Institute for Health and Clinical Excellence (NICE) issued guidance in December 2007 which confirmed that there is limited evidence to support the efficacy of thoracoscopic excision of mediastinal parathyroid lesions [111].

Negative preoperative Localization

The surgeon should have a clear plan prior to the intervention as to the means by which the abnormal parathyroid will be identified, e.g., if two normal glands were found on one side of the neck at the initial operation it is reasonable to explore the contralateral side first. If an enlarged parathyroid gland is found and excised and a fall in PTH confirms cure, the operation is terminated. If 'cure' is not confirmed then the exploration is continued, if necessary exploring both sides of the neck until biochemical cure is confirmed.

Cryopreservation of parathyroid tissue for future transplantation [112] or autotransplantation of parathyroid tissue should be considered in patients having total parathyroidectomy.

If exploration is negative, a thyroid lobectomy on the side of suspicion should be considered to remove suspected/unidentified intrathyroidal parathyroid lesions.

Hyperfunctioning Parathyroid Autograft

Patients with confirmed hyperfunctioning forearm autograft require excision of hyperfunctioning graft tissue and lifelong calcium replacement therapy.

Parathyromatosis

Removal of all abnormal parathyroid tissue/scattered nodules in the neck should be attempted. Parathyromatosis may be difficult to diagnose preoperatively and although color Doppler sonography can easily identify scattered deep and superficial hypoechoic, hypervascular lesions, they do not conform to typical anatomic locations of parathyroid glands [54]. Although a rare cause of recurrent RHPT control of the disease with surgical resection has been reported [53, 113].

Angiographic Ablation

Angiographic ablation is a nonsurgical alternative to standard mediastinal exploration that involves injection of ionic contrast material or alcohol into a previously identified arterial vessel feeding the abnormal parathyroid

Table 21.3. Anatomic location of abnormal parathyroid glands and results of reoperation for recurrent/persistent HPT

Locations	Wang (1977) [37]	Shen (1996) [119]	Jaskowiak (1996) [117]	Thompson (1999) [77]	Feingold (2000) [57]	Arnalsteen (2004) [81]	Gough (2006) [121]
Eutopic	29	48	113	103	14	28	19
Ectopic	78	54	109	26	47	46	26
Supernumerary	4	–	0	–	–	1	5
Multiglandular disease (%)	–	37	0	73	–	69	56
RLN injury (%)	2.7	1	1.3	0.8	–	–	–
Permanent hypocalcemia (%)	18	1	5	13		9	–
Cure rates (%)	91	95	96.8	88	98	97.6	98
Total number of patents	112	102	222	129	61	77	50

gland [114]. The hyperosmolar contrast material transudes into the interstitial spaces of the parathyroid and leads to ischemic insult and destruction of the gland. Angiographic ablation can be used in patients who are poor surgical candidates; however, experience with this technique is limited and the failure rate is as high as 40%, and tissue for histology cannot be obtained [115].

Patients who are unfit to have any form of surgical or interventional radiological procedure can be treated with medical therapy with biphosphonates and calcimimetics. Cinacalcet has been used successfully to lower PTH in recurrent RHPT [57, 59].

Success rates in seven published series of parathyroid reoperations for PHPT between 1977 and 2006 are 82–98%, with multiglandular disease identified in 37–73% of cases. The incidence of RLN injury varies between 0 and 2.7% and permanent hypocalcemia rates of 1–18% [40, 60, 77, 81, 116-118] (Table 21.3). A high number of missed glands wre found in eutopic sites [10, 81, 116–124].

Summary

The chances of cure are highest at the first operation, and it is therefore important to 'get it right the first time' [6]. Parathyroid surgeons should be familiar with the operative algorithm when an abnormality is not found at initial parathyroid exploration [104]. Confirmation of the biochemical diagnosis of HPT, examination of initial parathyroid localization studies, in conjunction with review of the operative findings and pathological examination of tissue removed at initial surgery are the initial key steps in the evaluation of a patient with recurrent/persistent HPT.

Further localization studies should be carried out if there are indications for reoperation.

The indications, risks, and benefits of reoperation should be weighed carefully against the patient's comorbidity.

Reoperation can be targeted to remove abnormal gland/s when localization tests are positive but more extensive exploration may be necessary if localization tests are negative or there is suspicion of multiglandular disease.

At surgery, the removal of all hyperfunctioning parathyroid tissue should be confirmed with frozen section and intraoperative PTH.

Reoperative parathyroid surgery can be a technically demanding procedure and should be undertaken by experienced endocrine surgical teams to maximize the rate of success [74].

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22

Management of Secondary and Tertiary Hyperparathyroidism

Jui-Yu Chen, Ling-Ming Tseng and Chen-Hsen Lee

Introduction

Secondary hyperparathyroidism (sHPT) is a condition that occurs when external factors stimulate the parathyroid glands to increase the secretion of parathyroid hormone (PTH), and develop mostly hyperplasia and/or adenomas of the parathyroid. The most common external factor is chronic renal failure (CRF) (i.e., renal hyperparathyroidism) [1]. Renal hyperparathyroidism could cause osteitis fibrosa, and other varieties of extra-osseous manifestations. Some consequences would bring patient poor life quality and even mortality [2].

Tertiary hyperparathyroidism (tHPT) is a state of autonomic excessive secretion of PTH developing from the secondary hyperplasia that occurs despite after restoration of renal function by dialysis or kidney transplantation [3]. tHPT is not a common disease process in the kidney transplant population, but it can cause damage of graft function that is not easily detected.

Pathogenesis

The major factors in the pathogenesis of sHPT consist of hypocalcemia, hyperphosphatemia, reduced 1,25 dihydroxyvitamin D3 (1,25-[OH] 2D3, calcitriol) production, altered PTH metabolism, skeletal resistance to PTH, and changed set-point in PTH production.

Before Kidney Transplantation

Hypocalcemia, resulting from phosphorus retention [4] and reduced calcitriol synthesis [5], has been regarded as the classic cause of sHPT. Besides, phosphorus retention directly promotes PTH synthesis and secretion [6]. Dietary phosphate load is found to affect the parathyroid cell cycle [7] and the responsiveness of parathyroid cells to extracellular Ca^{2+} concentration. The resistance of bone to PTH also plays a part in the pathogenesis of sHPT due to low level of calcitriol, phosphate retention, and downregulation of PTH bone receptors [8].

The PTH set point is dependent on the serum calcium concentration which can decrease the maximal PTH level by 50%. In uremic patient, there is a shift in the PTH set point rendering the parathyroid insensitive to the suppressive effects of calcium [9], and excessive PTH is secreted without moderate control mechanism. A novel phosphaturic hormone, fibroblast growth factor-23 had been reported to be implicated in the pathogenesis of renal osteodystrophy (ROD) [10]. The decreased responsiveness of parathyroid glands to vitamin D is also found in the pathogenesis of sHPT. It could in part be explained by the reduced vitamin D receptor (VDR) [11] and reduced calcium-sensing receptor (CaSR) expression in the patients [11, 12].

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After Kidney Transplantation

sHPT usually regresses after successful kidney transplantation due to the reversion of abnormalities in mineral metabolism attributing to parathyroid proliferation. Continuous hyperfunction of hyperplastic parathyroid glands is the main reason for hypercalcemia after kidney transplantation. Parathyroid autonomy, slow involution of parathyroid glands, nonsuppressible PTH secretion, abnormal PTH set point, and insufficient calcitriol secretion are important factors that may prevent the involution of the hyperplastic parathyroid gland even with a well-functioning kidney transplant.[13, 14, 15] The prevalence of persistent sHPT after kidney transplantation is seen in approximately 8.5–53% [13, 14]. Only few required operative reduction of parathyroid gland mass as a definitive treatment.

Clinical Manifestations

Classical clinical manifestations of sHPT consist of many varieties of skeletal and nonskeletal complications. ROD includes either osteitis fibrosa or mixed uremic bone-type disease, and nonskeletal toxicity includes the metastatic calcifications and skin lesions due to the disturbance of PTH and mineral metabolism.

Skeletal Disease

ROD-inducing bone loss remains the major cause of morbidity in uremic patients [16] and occurs as a consequence of bone-remodeling dysregulation. The severity varies and comprises pain, deformities to fractures. Bone pain is usually located at the lower back, hips, and legs while fractures commonly occur in long bones, vertebras, and ribs. The deformity manifestation arises mainly from vertebral fractures leading to kyphosis and lumbar scoliosis. Shortening of body height is usually a result of compression fractures of the vertebras.

Elevated levels of PTH would stimulate bone demineralization and lead to high bone turnover characterized by an enhanced number and activity of osteoclasts, resulting in increasing bone resorption. The classical histological pathology is osteitis fibrosa accompanied with reduced bone mass, increased nonlamellar bone, osteopenia, and fractures [17] (Fig. 22.1). A consequence of this is the release of calcium and phosphorus into the systemic circulation. In addition to the bone manifestation, ongoing absorption of calcium from the gastrointestinal tract during treatment with calcium-based drugs would lead to the propensity for metastatic calcification in soft tissues.

After the long-term use of aluminum-based phosphorus-binding agents, uremic patients would present with adynamic bone disease or osteomalacia [18]. Aluminum is absorbed by the intestines and rapidly transported into bones. Under those circumstances, aluminum accumulates in the mineralization front and prevents osteoid mineralization. Fortunately, the incidence of aluminum toxicity has been decreased because of the use of water purification for dialysate solutions and absence of aluminum in phosphate-binding agents.

Diagnosis of Uremic Osteodystrophy

Patients with high-turnover hyperparathyroid bone disease and low-turnover aluminum-associated bone disease display similar clinical and laboratory features. A misdiagnosis of osteitis fibrosa could lead to the decision of parathyroidectomy, and then worsen the bone condition of truly aluminum-related low-turnover bone disease [19]. It is important to differentiate these different conditions, and bone biopsies remain the most rational approach.

Extraskeletal Disease (Tissue Calcification)

There are two types of tissue calcification: metastatic and dystrophic calcification. Metastatic calcification occurs when calcium salt deposits in normal tissue whereas dystrophic calcification occurs in previously damaged tissue [20]. There are three major types of extra-skeletal calcification: visceral, periarticular, and vascular calcification. Visceral calcification includes lungs, myocardium, mitral valve, kidney, skeletal muscle, breast, and stomach. Periarticular calcification manifests as calcific periarthritis, and small-joint effusions. Vascular calcification involves small and large vessels, and calcification of penile artery may induce impotency.

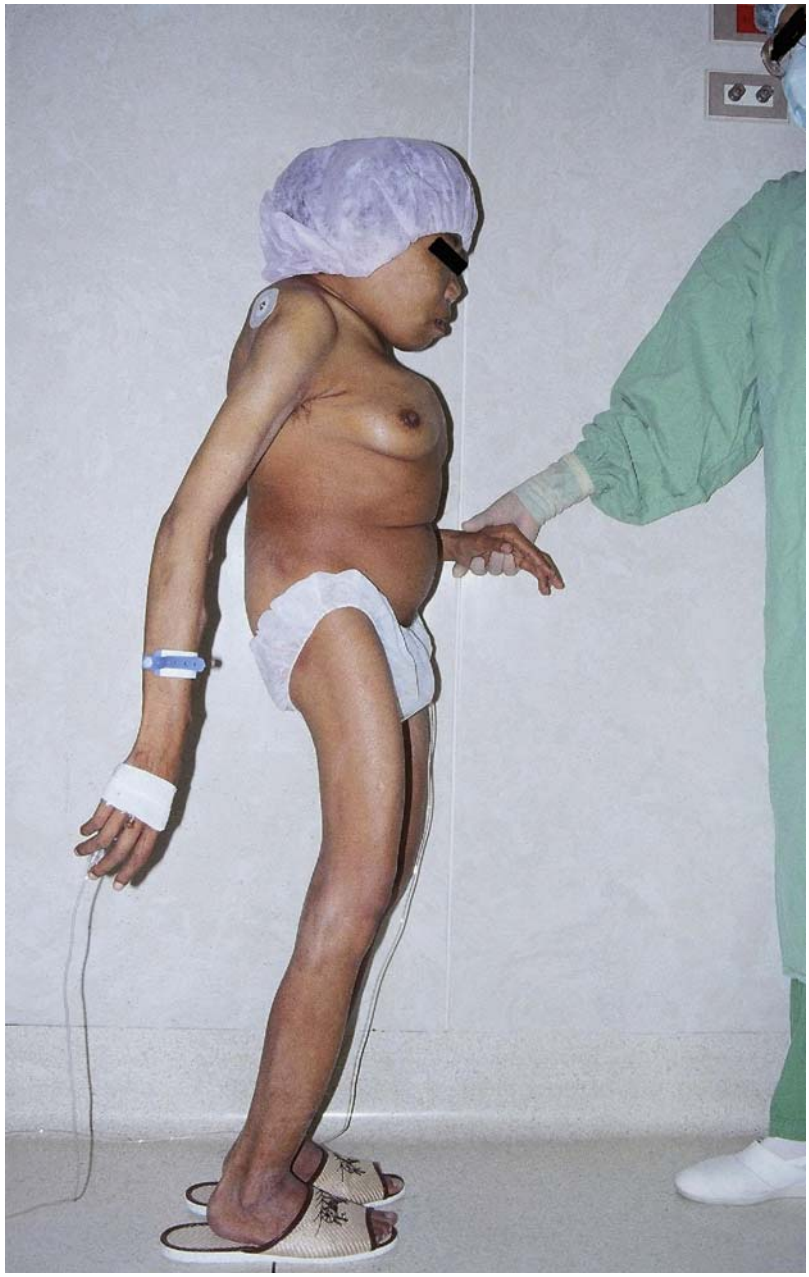

Fig. 22.1. Severe kyphoscoliosis in a patient with severe sHPT due to compression fracture of thoraco-lumbar vertebrae.

Cardiovascular Problems

Elevated PTH has been shown to exacerbate changes in cardiovascular structure and function. It is contributory to the high cardiovascular morbidity and mortality rates in uremic patients [21]. Besides, prolonged exposure to elevated PTH has been linked to high arterial blood pressure [22] and increasing levels of intracellular calcium attributes to the underlying mechanism.

The deposition of calcium and phosphorus in blood vessels in addition to arterial hypertension induces atherosclerosis [23]. Hemodialysis patients have a very high prevalence of vascular calcification of up to 83% (Fig. 22.2).

Hyperphosphatemia and hypercalcemia have been shown to promote calcification of vasculature (coronary artery included), myocardium, and cardiac valves [24]. Calcification of the electrocardiac conduction fibers may lead to variable degree of atrioventricular block (Fig. 22.3). Left ventricular hypertrophy (LVH) is seen frequently in uremic patients. It is the major cause of cardiac mortality associated with myocardial fibrosis, poor perfusion, and cell death [25]. Excessive PTH could lead to the development of LVH and reduced left ventricular ejection fraction [26]. It is believed that human fetuin-A deficiency may contribute to a decrease in vascular wall elasticity and is a potent cardiovascular risk factor [27].

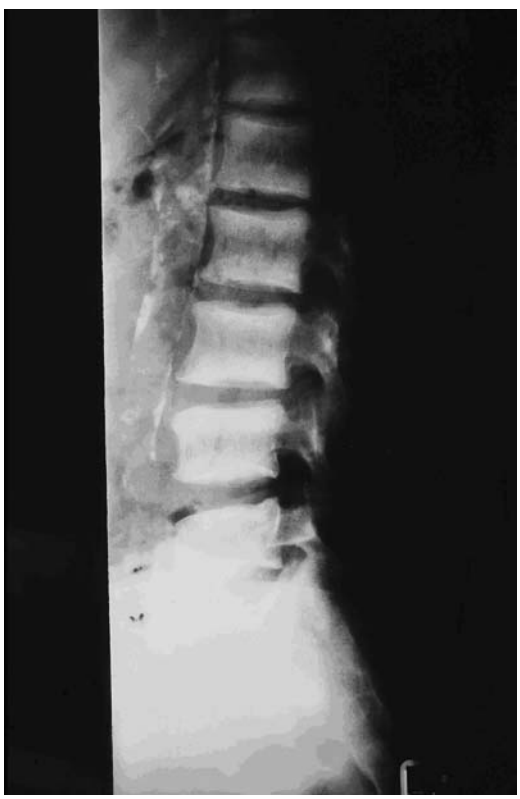

Fig. 22.2. Remarkable calcification of the aorta, splenic artery, etc., in a sHPT patient.

Metastatic Pulmonary Calcification

Calcification of the lung leads to impaired pulmonary function, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, and right-sided chronic heart disease. MPC was previously shown to be primarily amorphous whitlockite in composition, rather than the crystalline hydroxyapatite [20, 28]. Whitlockite is more likely to persist despite therapy, as opposed to hydroxyapatite, which tends to dissipate with appropriate therapy [28]. MPC could be diagnosed by high-resolution CT with high sensitivity [29], or Tc99m-MDP bone scan [20] Autopsy study revealed the pulmonary calcification occurred in the alveolar septae, bronchi, and vessels.

Pruritus

Pruritus is a common (>50%) disturbing symptom among patients on hemodialysis [30]. Serum phosphate, calcium, and magnesium and their ionic products are related with its development. The symptom may get dramatic improvement after parathyroidectomy (PTX) [31].

Calciphylaxis

Calciphylaxis (calcific uremic arteriolopathy) is an uncommon syndrome of disseminated calcification, resulting in both vascular calcification and skin necrosis (Fig. 22.4). The main histopathological finding is calcium deposits within arteriolar and small vascular walls, inducing endovascular fibrosis associated with fat necrosis. Lesions are characteristically located over the hands and fingers, lower extremities, and sometimes lower abdomen. The patients usually have a high Ca × P product but not necessarily extremely high PTH levels. Gangrene of distal limbs can lead to sepsis and death [32]. The prognosis for patients with calciphylaxis is poor with mortality approaching 50%. Some potential etiological factors have been identified including reduced serum levels of a calcification inhibitory protein α,2-Heremans-Schmid glycoprotein

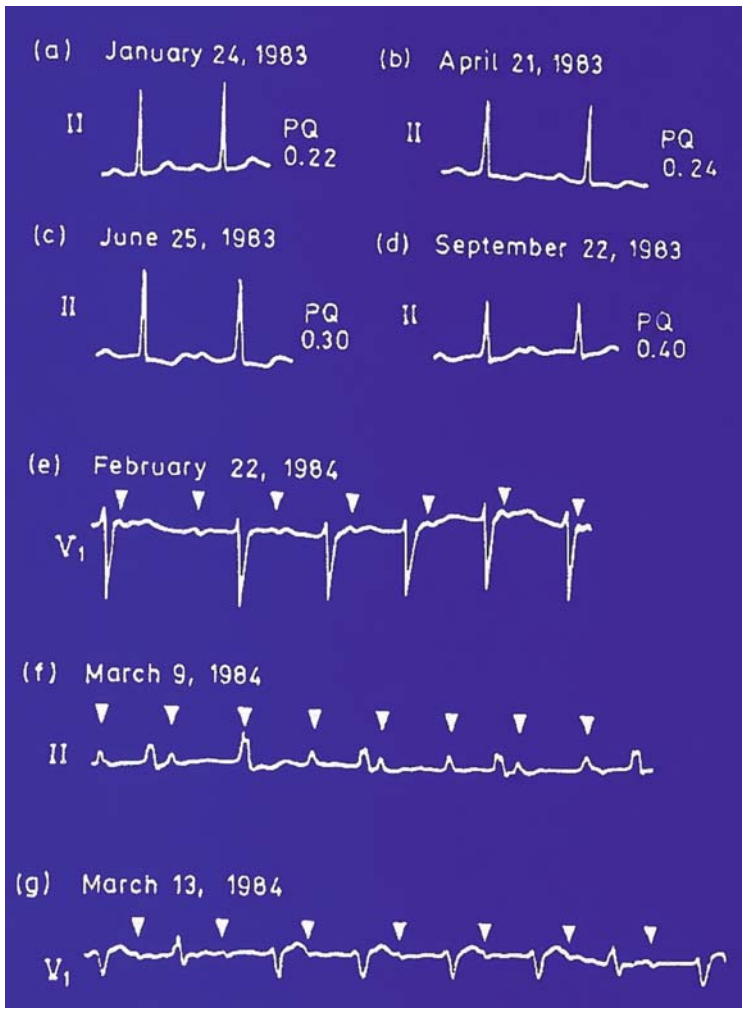

Fig. 22.3. Calcification of the electrocardiac conduction fibers may lead to variable degree of atrioventricular block. (a, b, c, d) first-degree A-V block; (e) second-degree A-V block (Wenkebach type); (f) ECG on admission to hospital; (g) alternating RBBB and LBBB.

(Fetuin-A) and abnormalities in smooth muscle cell biology in uremic patients [33].

Sexual Dysfunction

Sexual dysfunction is a common feature in both men and women. Disturbances include erectile dysfunction in men, menstrual abnormalities in women, and decreased libido in both sexes [34].

Anemia

Normochromic, normocytic anemia is a common complication in hemodialysis patients. Decreased erythropoietin production, aluminum toxicity, iron deficiency, infections, and increased hemolysis are important contributing factors [35]. Progressive HPT induces bone marrow resistance and reduces its response to erythropoietin treatment [36].

After Kidney Transplantation

tHPT may be difficult to be distinguished from primary HPT clinically because of similar serum chemistries; however, tHPT usually occurs in patients with CRF who have undergone a

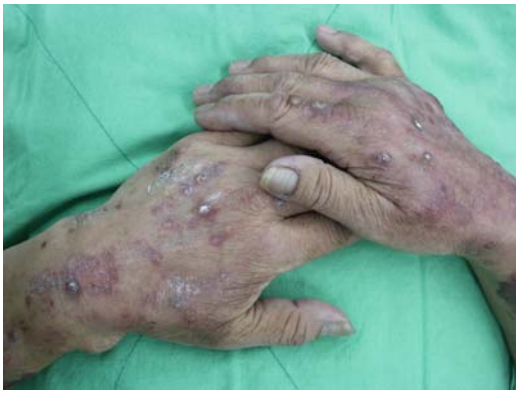

Fig. 22.4. Calciphylaxis-induced bilateral hand skin blisters and necrosis.

successful kidney transplantation. Both serum calcium and PTH are elevated but phosphorous may be low.

Management

In an attempt to improve the control of sHPT and clinical outcomes, the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) has recently published clinical practice guidelines for the management of bone metabolism and disease in chronic kidney disease [37] (Table 22.1). These evidence-based guidelines propose challenging new target levels for serum intact PTH (iPTH), calcium, phosphorus, and calcium–phosphorus product in patients with advanced chronic kidney disease mainly to avoid ectopic calcification and cardiovascular complications. However, most hemodialysis patients do not meet these goals. One large study of uremic patients from seven countries found that only 21% of patients satisfied the guideline's criteria for PTH concentration and 5% met the combined targets for Ca, P, PTH, and Ca × P product [38]. Eventually, some patients undergo parathyroid surgical intervention. When the parathyroid glands are enlarged and weigh more than 500 mg or exhibit nodular hyperplasia with monoclonal cell growth, vitamin D therapy might not effectively inhibit PTH oversecretion [39]. Such severe sHPT frequently causes hypercalcemia and hyperphosphatemia that consequently increase the risk of cardiovascular morbidity and mortality.

Table 22.1. National Kidney Foundation K/DOQI (Kidney Disease Outcomes Quality Initiative) targets for intact parathyroid hormone(i-PTH), calcium, phosphorus, and calcium-phosphorus (Ca × P) product in uremic patients

Variable	Target Range
Serum i-PTH	150–300 pg/ml (16.5–33.0 pmol/l)
Total serum calcium	8.4–9.5 mg/dl (2.10–2.37 mmol/l)
Serum phosphorus	3.5–5.5 mg/dl (1.13–1.78 mmol/l)
Ca × P	<55 mg^2/dl^2(<4.5 mmol^2/l^2)

Medical Treatment

The aim of medical treatment of sHPT is to prevent progression from diffuse to nodular hyperplasia. In order to avoid progression of sHPT, pathogenetic factors should be sought and eliminated [40]. Treatments of metastatic pulmonary calcification (MPC) include the correction of Ca × P product, parathyroidectomy, and renal transplantation [20]. Biophosphonate could be employed to stop the progressing of calcification [41]. In patients with calciphylaxis condition, the therapeutic strategy is to normalize the high Ca × P products with phosphate binders initially [42]. When calciphylaxis is complicated with advanced renal hyperparathyroidism, PTX should be performed promptly. A prospective study by Park et al. confirmed the finding that PTH-suppressive calcitriol therapy led to a regression in myocardial hypertrophy in dialysis patients [43].

Surgical Treatment

Prerenal Transplantation

Although sHPT could be effectively treated medically, medical therapy does not always work in achieving adequate control of serum PTH, calcium, phosphorus, and Ca × P product. Surgical PTX is indicated for severe sHPT associated with hypercalcemia and/or hyperphosphatemia but not responsive to medical approaches. The K/DOQI guideline (2003) [44] proposes surgical treatment for severe sHPT as follows: PTX is recommended for patients with severe HPT (a persistent serum level of iPTH $>$ 800 pg/ml, 88.0 pmol/l), associated with

hypercalcemia and/or hyperphosphatemia that are refractory to medical treatment. An additional indication for parathyroidectomy is the presence of calciphylaxis with an elevated PTH level of >500 pg/ml since it is a very serious complication in uremic patients [45]. These recommendations emphasize the avoidance of ectopic calcification and cardiovascular complications resulting from hypercalcemia, hyperphosphatemia, and a persistent high PTH level [46]. Besides, according to the algorithm of the Association of European Dialysis Transplantation (EDTA), the size of the parathyroid gland is one of the factors to be considered as the indications for surgery [47] (Table 22.2). Besides calciphylaxis, patients with high bone turnover, osteitis fibrosa on X-ray, severe symptoms of sHPT, progression of ectopic calcifications, progression of bone loss, and anemia resistant to erythropoietin should be advised to have surgical intervention [48].

Posttransplantation

Surgical treatment is the only curative therapy for tHPT [49, 50, 51]. Successful surgical intervention for sHPT and tHPT significantly reduces preoperative symptoms and leads to recovery of bone disease. Surgery is usually reserved for patients having symptoms of HPT refractory to medical treatment [52, 53]. Indications for surgery include persistent symptoms of hypercalcemia and/or renal graft calculi formation after a successful renal transplantation. Ultimately, 1.6–3% of all kidney recipients may require parathyroidectomy, as the definitive treatment for tHPT [54].

The indication of PTX for asymptomatic hypercalcemia alone after kidney transplantation is still controversial. Mild hypercalcemia alone is not a serious threat to the patient. Early reports showed that high PTH and hypercalcemia have detrimental effects on graft function and recommended early aggressive PTX for posttransplant HPT, as the association of renal stones with long-standing hypercalcemia [55]. Other studies found that posttransplantation hypercalcemia, occurring early after the transplant, mostly resolved spontaneously in the first month after kidney transplantation [56]. Thus, many investigators recommended conservative approach to posttransplant hypercalcemia, with PTX reserved for patients with progressive symptomatic disease and/or roentgenographic findings, those with an asymptomatic persistent hypercalcemia (greater than 12.0 mg/dl) for more than 1 year after the transplant, or those with acute hypercalcemia (calcium >12.5 mg/dl) in the immediate posttransplant period [57].

Table 22.2. Overall Indications for PTX

K/DOQI guideline
1. High level of PTH (intact PTH > 800 pg/ml)
2. Hypercalcemia
3. And/or Hyperphosphatemia
4. Condition: calciphylaxis with elevated PTH levels (>500 pg/ml)
EDTA (European Dialysis and Transplant Association): Detection of enlarged parathyroid glands by ultrasonography (volume of the largest gland > 500 mm3)
Other indications
1. High bone turnover, osteitis fibrosa
2. Severe symptoms of SHPT
3. Progression of ectopic calcification
5. Progression of bone loss
6. Anemia resistant to therapy

Preoperative Care

Medication and Preoperative Image Studies

The control of hyperkalemia, hypomagnesemia, hypervolemia, hypertension, and cardiovascular disease in uremic patient is mandatory to avoid perioperative complications.

Localization

Ectopic parathyroid glands may be pitfalls in attempts to detect all parathyroid glands, especially over mediastinal, intrathyroidal, and undescended glands. Ultrasound (US) is effective for detecting glands in the area around and within the thyroid lobes. Glands weighing more than 200 mg can be recognized by US. 99mTc sestamibi-scan (mibi-scan) is positive in 88% patients; however, it is difficult for a mibi-scan

to visualize all the diseased glands. Usually, only 1–2 dominant glands are visualized [58]. A preoperative neck US study also helps to detect any coexistent thyroid nodule or tumor disease.

Surgical Management

Type of Surgical Procedure

Three different surgical procedures are recommended in the K/DOQI guideline: subtotal PTX (removal of three and a half glands and leaving half a gland remnant in the neck), total PTX with autotransplantation (TPTX+AT) of some of the excised tissue into defined areas (forearm muscle, anterior tibial muscle or subcutaneously, and total parathyroidectomy without autotransplantation (TPTX). Not one technique appears to provide superior outcomes [59, 60]. Mortality and morbidity do not differ significantly between TPTX+AT and subtotal PTX [61].

Although TPTX alone provides a feasible therapeutic option, the procedure alone would carry with the potential complication of adynamic bone disease or severe hypocalcemia requiring lifelong vitamin D and oral calcium medications. It is not the procedure of choice in patients who may subsequently receive a kidney transplant. Therefore, subtotal PTX or TPTX+AT, both supplemented with thymectomy, are currently considered as the standard procedures in the treatment of sHPT [61, 62]. If a subtotal PTX is planned, the smallest parathyroid is selected to preserve. An approximately 50–70 mg remnant would be left with its blood supply and is marked with nonabsorbable material, e.g., hemoclips. If a total PTX with autotransplant would be arranged, all the glands over neck (usually four glands) are resected and the most suitable gland (one less likely to have severe nodular hyperplasia) is selected for immediate autotransplant. A 100-mg portion of the gland is sliced into 1-mm fragments and 10–20 fragments are placed into several separate intramuscular or subcutaneous pockets in the nondominant forearm. These pockets are closed with nonabsorbable material.

Subtotal Parathyroidectomy (SPTX)

Theoretically, SPTX has the advantage of less postoperative hypocalcemia. The risk of persistent hypocalcemia is less than 1% [63]. However, since the pathophysiological condition of CRF and maintenance dialysis continues, the growth stimulus persists and may cause recurrent sHPT of the remnant, which increases with time [64]. The success of SPTX depends on size and pathology of the remnant. Nodular remnant is likely to grow recurrently. An adequate mark on the parathyroid remnant facilitates the resection of the target lesion during reoperation.

Total Parathyroidectomy and Autotransplantation (TPTX+AT)

The advantage of total PTX with forearm autograft is that the recurrent parathyroid tissue can be removed from the forearm with less morbidity and can be performed under local anesthesia. Besides, the function of grafted parathyroid tissue can be detected by comparing the PTH levels at grafted and nongrafted arms, and the parathyroid function can be easily controlled by changing the amount of parathyroid tissue used for the autograft [48]. Therefore, total PTx with a forearm autograft is considered a preferable operative procedure in sHPT patients who continue with hemodialysis for a long time [48, 65]. Since the graft function does not build up immediately, a period of postoperative hypocalcemia usually occurred after TPTX+AT. Appropriate graft function is generally delayed several days to 3 months postoperatively. Normocalcemic patient just after operation should be considered as having an incomplete total PTX with supernumerary glands in the neck or mediastinum [66]. Some preferred grafting the parathyroid chips in the four quadrants of a subcutaneous pocket to avoid the disadvantage of muscle damage if graft-dependent HPT occurs and graft debulking is needed. It remains a problem to differentiate a supernumerary gland from a graft-dependent HPT or a combination of both for patients undergoing TPTX+AT. A US or mibi-scan of the graft site may visualize the hyperfunctioning graft especially if there are palpable subcutaneous nodules at the graft site. To avoid persistent HPT, detecting and removing all parathyroid glands at initial operation is essential but may be difficult to accomplish for supernumerary or ectopically located parathyroid glands. Routine

exploration and excision of the fat tissue surrounding the glands, removal of as much bilateral thymic tongue, and opening bilateral carotid sheaths to detect any glands around the carotid artery, trachea, and esophagus are recommended [65].

Surgical Intervention for tHPT

The surgical procedure for tHPT remains controversial. Some surgeons prefer bilateral neck exploration with subtotal or total parathyroidectomy and autotransplantation based on the belief that tHPT is usually due to multiple hyperplastic parathyroid glands and patients who have initial limited parathyroidectomy have a higher risk of persistent or recurrent tHPT [67, 68]. However, some investigators have reported that 2.6–32% of tHPT may have disease limited to single or double adenomas, and propose resection of only the enlarged glands after a bilateral neck exploration [69, 70]. Meanwhile, recent advances in radioguided parathyroidectomy, advanced imaging, and intraoperative PTH testing have facilitated a focused surgical approach as in the management of patients with primary HPT. PTX by unilateral approach under local anesthesia may be of value when preoperative localization studies show a single gland enlargement [70, 71].

Applications of the Intraoperative PTH Assay

Intraoperative measurement of PTH (IOPTH) using a quick assay 15–30 min after removing all parathyroid glands is performed to assess the completeness of parathyroid surgery [72]. The use of IOPTH has been controversial in the application of PTX for renal HPT. The major cause could exist in the variable PTH degradation kinetics with renal disease. There were studies that revealed no correlation between IOPTH and the PTH obtained on postoperative Day 1 [73]. However, others showed an average of 85% decline from the baseline for those with complete TPTx [74].

Due to high risk of recurrent laryngeal nerve injury in reoperation procedures and for the more accurate localization, jugular venous sampling for PTH determination is advised to regionalize the hypersecreting parathyroid tissue to one side of neck during reexploring operations [75].

Other Invasive Treatment

Intraparathyroid Injection of Alcohol or Vitamin D

Ultrasound-guided percutaneous ethanol or active vitamin D analog injection into parathyroid glands has been performed [76] in recent few years in few institutions. Repeated active vitamin D injections into parathyroid glands were reported to be effective in suppressing PTH secretion. Percutaneous injection of ethanol or active vitamin D analogs could also reduce the size of enlarged parathyroid glands. The induction of apoptosis of hyperplastic parathyroid cells and the upregulation of VDR on parathyroid cells by exposure to extremely high vitamin D concentrations have been shown to be the mechanisms underlying the reduced volume of parathyroid glands [77].

However, advanced sHPT is often associated with multiple parathyroid hyperplasia and is not easily controlled by alcohol injection. Besides, palsy of the recurrent laryngeal nerve is not a negligible complication of this procedure. As alcohol injection gives rise to adhesions of fibrous tissue, the identification of parathyroid tissue and the recurrent laryngeal nerve would be difficult in subsequent exploration [78]. Alcohol injection could be considered only for selected patients in whom only one gland is substantially enlarged, and those with high surgical risk or severe deformity of the cervical vertebrae limiting an extensive neck exploration [79].

Complications of Parathyroidectomy

The mortality after PTX for sHPT is from 0.15 to 3.1%. Short-term postoperative mortality rate after PTX is about 3.1%, and long-term-related risks of death among patients after PTX is estimated to be 10–15% [80]. Much mortality was related to chronic heart failure [79, 80]. The injury of recurrent laryngeal nerve was less

than 2%, and wound bleeding was less than 0.3% [63]. After PTX, there are dramatic reductions in PTH, calcium, and phosphate levels in more than 95% of patients [81, 82]. There are some important conditions that could be encountered:

Transient Hypocalcemia

Hypocalcemia occurs in 20–85% uremic patients with sHPT after PTX. Numbness, paresethesia, and tetany cramp could be the symptoms related. After PTX, the serum calcium will drop rapidly, as autografted parathyroid tissue does not function well immediately. Usually patients have severe hungry bone syndrome, because calcium and phosphorus would move from the blood for bone formation [83].

In the K/DOQI guideline the method of calcium supplementation was described in detail. Calcium-replacement therapy is advised in the condition of transient hypocalcemia. Vitamin-D as well as intravenous and oral calcium replacement should be administered in severe hypocalcemia patients.

Permanent Hypocalcemia (hypoparathyroidism)

The prevalence of permanent hypoparathyroidism is from 4 to 12%. Nonfunctioning of autograft parathyroid tissue is the major cause of permanent hypoparathyroidism. We could recognize the functioning by comparing serum PTH levels from both antecubital veins. A PTH gradient over 1.5 times between the grafted and the nongrafted arm indicates a functioning graft [83]. Re-transplantation with cryopreserved parathyroid tissue is limited in success rate. Patients with permanent hypocalcemia should be provided with vitamin D and calcium supplement for life.

Persistent and Recurrence Hyperparathyroidism

The incidence of persistent or recurrent hyperparathyroidism is from 2 to 12% [84, 85, 86]. Most are due to the incomplete PTX in the initial operation. There are many possible causes considered, including the origins from autograft (graft dependent HPT), supernumerary gland in the neck or mediastinum, metastasis of parathyroid tissue in the lung, and cell implantation due to ruptured grand surrounding the thyroid gland (parathyromatosis) [78]. Before a second operation, recognition of the origin is important. At first, we should determine whether the recurrence is graft dependent or nondependent, for which Casanova's procedure is a useful test [87]. When the PTH level does not drop significantly by blockade of the blood stream in the grafted arm, we can assume that the origin of PTH hypersecretion is not from the autografted tissue but more likely from the residual parathyroid tissue in the neck or mediastinum. The recurrence after TPTX+AT is mostly graft dependent. Partial resection of the graft is advised after ultrasound or mibi-scan of the graft. On the other hand, if the recurrence is notgraft dependent, residual parathyroid tissue should be localized or regionalized before reexploration of neck or mediastionotomy. US and mibi-scan can be employed initially. If the two imagings fail, CT and MR imaging should be considered. Occasionally, a selective angiography or selective venous sampling for PTH is needed in difficult cases.

Clinical Course after Successful Parathyroidectomy

After PTX, symptoms such as bone and joint pain, irritability, sleeplessness, and pruritus decrease overnight in our experience and also others [31, 65]. The improvement of muscle weakness depends on the degree of preoperative muscle wasting.

Bone Disease (Osteoporosis)

Rapid decrease in PTH after PTX would suppress bone resorption and cause a transient marked increase in bone formation, and an increase in normal lamellar osteoid seams [88]. The bone mass density of the lumbar spine can be significantly increased with timely postoperative supplementation with vitamin D and calcium [89]. The mineral content in trabecular bone measured by X-ray absorptiometry increases about 10% after PTX, but in cortical bone the increase is only 2–3% [90]. Biopsy

studies have shown that bone resorption is immediately suppressed and bone formation is accelerated after PTX [91].

Anemia

As increased PTH levels may have some direct effects on erythropoiesis, red cell survival, and induce bone marrow fibrosis. Zingraff first reported that parathyroidectomy improved the anemic status of CRF patients by surgical suppression of PTH secretion. Medical suppression of PTH oversecretion by intravenous calcitriol supplement has similar effects on the anemia observed in dialysis patients. It is therefore early control of PTH secretion is crucial for preventing worsening of anemic status [92, 93].

Cardiovascular Condition

The benefit for hypertension control after surgery is controversial. PTX has been found to lower blood pressure in a significant proportion of sHPT patients, but there was no pressure change observed in the study of Ifudo et al. [94]. Successful PTX could improve nonvisceral calcification in 50–60%, but the change of vascular calcification is definitive [95]. Bleyer and his colleagues observed decrease in vascular calcification [96] but, on the contrary, no benefit or even worsening was reported by de Francisco et al. [97]. PTX rarely affects vascular calcification but usually diminishes nonvascular calcium deposits [96]. It is therefore important that PTX should be performed at an early stage before the calcification has become progressive [48, 98]. PTX in uremic patients with sHPT has led to a significant improvement of left ventricular ejection fraction and function [98].

Summary

Poor control of renal HPT would bring serious outcomes from the skin itching to cardiovascular impairment. Parathyroidectomy should be considered as early as possible if the sHPT progresses despite medical treatment. After successful parathyroidectomy, sHPT-related symptoms usually improve. It is believed that early intervention should be performed if progressive hyperparathyroidism is suspected after a successful kidney transplantation to avoid further renal osteodystrophy, extra-osseous calcification, and failure in renal graft function.

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23

Parathyroid Carcinoma

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Introduction

Parathyroid carcinoma is a rare cause of primary hyperparathyroidism (PHPT) (<1%) and is usually associated with more severe clinical manifestations than its much more common benign counterpart, the parathyroid adenoma [1–3]. It usually has a rather indolent course with the diagnosis of malignancy often made only in retrospect when the disease recurs locally or at distant sites. The delay in recognition is due to the fact that the histology of the tumor tissue can be equivocal or frankly misleading [2, 4]. The prognosis of parathyroid carcinoma is quite variable, but most patients succumb to the effect of PTH oversecretion by metastases and ensuing severe hypercalcemia, not to the bulk of tumor tissue per se. A successful resection of all tumor tissue at the time of initial surgery is a key determinant to a successful outcome. Therefore, identifying clinical features that might suggest malignancy can be most helpful in terms of the surgical procedure. The surgeon can also be helpful by identifying gross characteristics of the malignant parathyroid tissue. In recent years, major advances have been made in the understanding of the molecular pathogenesis of parathyroid carcinoma [5–9]. This new knowledge has led to the development of diagnostic markers that show promise when the histology is ambiguous [10–13]. Moreover, there is the hope that greater understanding of the pathogenesis of parathyroid cancer will lead to the development of new therapeutic strategies.

Incidence

More than 290 cases of parathyroid carcinoma were described in the English literature between 1930 and 1992 [3]. Subsequently, more than 100 cases have been reported [3]. The largest series was collected by the National Cancer Database that reported the majority of these cases [14]. In most series of PHPT, parathyroid carcinoma accounts for less than 1% of all cases [1], but an incidence as high as 5% has been reported in two groups [15, 16]. This higher incidence of carcinoma may be related to geographic differences or, more likely, to varying criteria for its diagnosis.

Different from benign parathyroid disease in which females predominate over males by 3–4:1, the incidence of parathyroid cancer is equally divided between the sexes. The age at diagnosis is 10 years earlier than the typical age when the benign form of PHPT surfaces (mid-40s vs mid-50s).

Etiology

The etiology of parathyroid carcinoma is unknown. Prior neck irradiation is a risk factor [17, 18], but the role of radiation is not clear.

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Parathyroid carcinoma has also been rarely reported in patients with long-standing secondary hyperparathyroidism, namely in patients undergoing hemodialysis for chronic renal failure [19]. One case, however, has also been reported in a patient with celiac disease and long-standing secondary hyperparathyroidism [20]. However, it is not clear in these cases whether the pathology met criteria for a parathyroid malignancy.

Parathyroid carcinoma has also been reported in association with hereditary syndromes of hyperparathyroidism [21–25]. It occurs in as many as 15% of patients with the hyperparathyroidism-jaw tumor (HPT-JT) syndrome [26]. HPT-JT is a rare autosomal dominant disorder in which PHPT is due to neoplasms of one or more parathyroid glands. Cystic changes in the parathyroid tumors are common, thus accounting for an alternative description of this variant as cystic parathyroid adenomatosis [27]. Ossifying fibromas of the maxilla and mandible are found in 30% of patients; renal cysts, hamartomas, and Wilm's tumors are seen less commonly [5]. In another familial syndrome, namely familial isolated PHPT, parathyroid carcinoma has been reported [28, 29]. A few recent reports have suggested that parathyroid carcinoma, as defined pathologically, may occur in a setting of MEN1 syndrome and/or tumors carrying somatic *MEN1* mutations [30, 31]. However, some of these reports should be interpreted with caution because recurrent disease in the MEN1 may be tenacious when it occurs at the site of previous surgery, thus mimicking a parathyroid carcinoma. Thus, it is conceivable that at least some of these cases could be "false positives" on the basis of conventional pathology, but without the clinical expression of parathyroid carcinoma in patients with MEN1. Only one case of parathyroid carcinoma has been reported in patients with MEN2A syndrome [32].

Molecular Pathogenesis

In 1994 Cryns et al. [33] showed lack of expression of retinoblastoma (Rb) protein in parathyroid cancer and suggested that inactivation of the Rb gene might be involved in the pathogenesis of parathyroid carcinoma. Based on this finding, loss of Rb protein was proposed as a tool for the diagnosis of parathyroid malignancy. Since that proposal, however, contradictory results have been reported by other investigators [34, 35]. We further evaluated the role of the Rb gene as a potential tool to distinguish between benign and malignant parathyroid disease by evaluating loss of heterozygosity (LOH) at this locus and by Rb immunohistochemistry [36]. We showed that Rb gene alterations are not specific for parathyroid cancer. Overall, our data do indicate that retention of Rb heterozygosity excludes malignancy which is also suggested by the combined finding of LOH and lack of Rb protein expression. It is worth noting that the same authors who previously showed that Rb1 inactivation is a key factor in the pathogenesis of parathyroid carcinomas have recently found no microdeletion, insertions, or point mutations in the coding or promoter regions of the *Rb* gene in a small series [37]. These results suggest that loss of Rb protein in parathyroid carcinomas could be due to epigenetic effects (e.g., hypermethylation) or secondary to other genetic alterations.

Cryns et al. have found evidence for the involvement of p53, another tumor suppressor gene, in parathyroid cancer [38]. They showed allelic loss of p53 and abnormal p53 protein expression in some cases of parathyroid carcinoma.

Overexpression of cyclin D1, a cell cycle regulator, is present in the majority of parathyroid carcinomas (~90%), but it is unclear whether this is a causative feature or an epigenetic effect [12, 39].

In addition, losses or gains in various chromosomal loci have been identified in parathyroid carcinomas, suggesting that genes located in these chromosomes might be involved in aberrant parathyroid growth.

Recently, major advances in the understanding of parathyroid cancer pathogenesis have been made by the cloning of the Hyperparathyroidism 2 gene (*HRPT2*, CDC73), previously known as chromosome 1 open reading frame 28 (*Clorf 28*) [5], as the gene responsible for HPT-JT.

Evidence points to a strong association between *HRPT2* mutations and parathyroid carcinoma. *HRPT2* is the target for germline mutation in the majority of families with the rare HPT-JT [5, 40, 41], in which, as noted, parathyroid carcinoma occurs at higher frequency than in sporadic PHPT series (15 vs <1%). Similar germline mutations occur in a subset of kindreds with familial isolated hyperparathyroidism [5, 8, 42–48]. The role of the *HRPT2* gene in

the pathogenesis of sporadic parathyroid carcinoma was first demonstrated by Howell and coworkers in 2003 [6]. In their study, *HRPT2* mutations were detected in the coding region of the gene in four of four parathyroid carcinomas and in none of 25 sporadic parathyroid adenomas. Subsequently, Shattuck et al. [7] found *HRPT2* mutations in 10 of 15 patients with apparently sporadic parathyroid cancer. Our group has identified *HRPT2*mutations in 9 of 11 parathyroid carcinomas [8, 12]; in this study we also investigated four sporadic atypical adenomas but no *HRPT2* mutations were identified in these tumors. The majority of the mutations were predicted to inactivate the protein, parafibromin, for which this gene codes. Of particular interest was the demonstration that *HRPT2* mutations in parathyroid carcinomas of six patients were germline [7, 8, 12]. This finding suggests that a subset of patients with apparently sporadic parathyroid carcinomas may have the HPT-JT syndrome, a variant of this syndrome, of some other genetic disorder associated with this genetic abnormality. The strong association between *HRPT2* mutation and parathyroid malignancy suggests that this molecular event has a pathogenic role for most sporadic parathyroid carcinomas. It is noteworthy that all the three reports of this gene in sporadic parathyroid malignancy included cases in which the diagnosis was clear. Indeed, the diagnosis of parathyroid carcinoma was defined generally by presence of either distant metastases and/or local invasion of surrounding organs, and/or vascular invasion, and/or recurrences after initial surgery. Combining the results of these studies, the prevalence of *HRPT2* mutations in sporadic parathyroid carcinomas is 76.6% (Fig. 23.1). It is possible that inactivating mutation in noncoding or regulatory regions could also be implicated in the pathogenesis of sporadic parathyroid carcinoma and might be present in those cases in which alterations in the coding regions of the gene are not detected. A recent study by Haven et al. [49] found *HRPT2* inactivating mutations in only 4 cases of 27 (15%) parathyroid carcinomas. These tumors were classified as malignant on the basis of pathological criteria alone without the requirement for clinically malignant behavior. Moreover, in this study, the mutational analysis was limited to exons 1, 2, and 7, which admittedly harbor 85% of all known mutations.

HRPT2 mutations are rarely found in sporadic parathyroid adenomas. Carpten et al. [5] detected mutations in only 2 of 47 parathyroid adenomas that were selected for their cystic features, a specific characteristic of parathyroid tumors in the HPT-JT syndrome. We found a single mutation among 35 sporadic adenomas, which were selected for the lack of LOH at 11q13

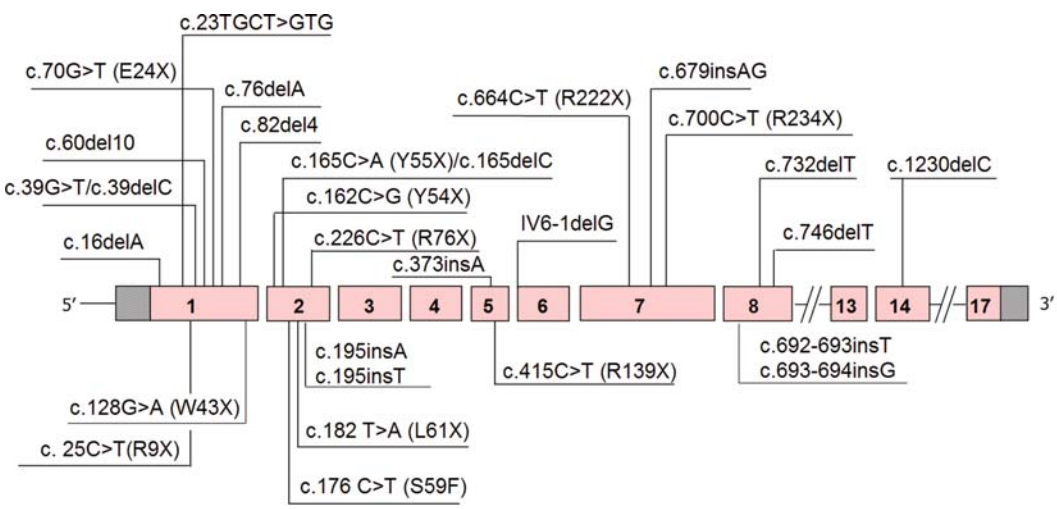

Fig. 23.1. Schematic representation of *HRPT2* gene. Locations of known *HRPT2* mutations in sporadic parathyroid carcinomas. (Reproduced from J Bone Miner Res 2008;23:1869–1880 with permission of the American Society for Bone and Mineral Research. [3])

[8]. Two studies of unselected parathyroid adenomas (85 tumors) failed to detect any *HRPT2* mutations [6, 9]. Taking all available data in parathyroid adenomas together, the overall prevalence of *HRPT2* mutations is 1.8% (3 of 167). Krebs has suggested an even lower estimate, 0.8% (1/120) on the basis of the results of Howell [6], our group [7] and Krebs [50]. These observations indicate that *HRPT2* mutations have a very limited, if any, role in the pathogenesis of typical sporadic parathyroid adenomas.

Clinical and Laboratories Features

The clinical manifestations of parathyroid carcinoma are primarily related to the effects of markedly elevated serum PTH levels rather than to local infiltration, distant spread, or sheer mass of neoplastic cells. Occasionally parathyroid carcinomas may be nonfunctional [47].

The typical clinical picture is characterized by signs and symptoms of severe hypercalcemia, with renal involvement (nephrocalcinosis, nephrolithiasis, impaired renal function) in up to 80% of patients as well as bone involvement (osteitis fibrosa cystica, subperiosteal resorption, "salt and pepper" skull, diffuse osteopenia) in up to 90% [1, 3]. The combination of both renal and bone manifestations at the time of presentation suggests the possibility of parathyroid malignancy because in benign PHPT, overt bone and stone disease is uncommon. Despite these clinical features which may suggest a malignant tumor, the challenge to the clinician rests upon identifying the patient with malignant disease, particularly since the benign counterpart is so much more common. A few helpful clinical clues would favor a malignancy [1, 3]:

- *male gender*. There is no sex preference, whereas the female:male ratio in benign PHPT is 3–4:1.This is not particularly helpful, however, in an individual case.
- *relatively young age*. The average decade of malignant parathyroid disease is 40–50, about 10 years younger than the usual patient with adenoma. However, the Mayo Clinic experience [51] and that of National Cancer Database [14] indicate that the average age may be higher, in the 50–60 decade.
- *markedly elevated serum calcium and PTH*. Most patients with typical parathyroid adenomas have serum calcium levels within 1 mg/dl above the upper normal limit and are asymptomatic. In parathyroid cancer, the serum calcium levels are usually in excess of 14–15 mg/dl. These patients are typically symptomatic with weakness, fatigue, depression, nausea, polydypsia, and polyuria. Bone pain and renal colic may be present. As might be expected, PTH levels are markedly elevated (typically 10 times normal) in patients with parathyroid carcinoma in contrast to benign disease in which PTH levels are typically only 1.5- to 2-fold above normal.
- *size of the parathyroid lesion at initial surgery*. A parathyroid carcinoma size is usually large, over 3 cm in diameter, and strongly adherent to adjacent structures. The gross appearance is often a major clue to the histological diagnosis.

A summary of the typical features differentiating parathyroid carcinoma from adenoma is reported in Table 23.1.

It is important that parathyroid carcinoma is considered in the differential diagnosis of PTH-dependent hypercalcemia when clues are present, because the morbidity and mortality associated with this diagnosis are substantial. Better outcomes are associated with complete resection of the tumor at the time of initial operation [1–3]. Unfortunately, in the majority of cases the diagnosis of parathyroid carcinoma is made in

Table 23.1. Clinical features suggestive of parathyroid carcinomas vs benign PHPT*

	Parathyroid carcinoma	Benign PHPT
Average age (year)	48	55
Female:male ratio	1:1	3–4:1
Serum calcium (mg/dl)	>14	≤11.2
PTH	Markedly elevated	Mildly elevated
Palpable cervical mass	Common	Rare
Renal involvement (%)	30–80	4–18
Skeletal disease (%)	35–91	<5
Concomitant renal and skeletal disease	Common	Rare

Modified from Shane et al. [1]

retrospect when hypercalcemia recurs due to parathyroid hormone secretion by local tumor or distant metastases.

Recent data by us have demonstrated that in some patients with parathyroid cancer, a new PTH moiety is overproduced, i.e., an N-terminal PTH molecule (N-PTH), distinct from the intact human 1-84 PTH, which is recognized in a third-generation assay of "whole" PTH (wPTH; the 1-2 epitope) [52]. The clinical implications of this finding in parathyroid carcinoma await additional studies in a large series of patients with an emphasis on N-PTH's biological activity. Serum alkaline phosphatase activity is also substantially higher in patients with parathyroid carcinoma than in those with parathyroid adenoma, in whom serum levels are generally at or only slightly above the upper limit of the normal range. α and β subunits of hCG may be elevated in patients with parathyroid cancer but not in those with benign tumors [53]. On physical examination, up to 75% of patients with parathyroid carcinoma have a palpable neck mass [54]. Since a palpable parathyroid gland is rare in the benign disease, this finding should automatically raise the suspicion of cancer. Parathyroid cancer should also be suspected in a hypercalcemic patient, who presents with recurrent laryngeal nerve palsy, without a history of prior neck surgery.

The classical target organs of PTH, the kidney, and the skeleton, as noted before, are affected with greater frequency and severity in patients with parathyroid carcinoma [1, 3] than in patients with benign PHPT. Indeed, in benign parathyroid disease, the prevalence of renal involvement, including nephrolithiasis, nephrocalcinosis, and impaired glomerular filtration, is less than 20%. Renal colic, on the other hand, can be the presenting complaint in the patient with parathyroid carcinoma. Bone pain and pathological fractures are also common features of parathyroid malignancy. In addition to the kidney and the skeleton, other organs are frequently affected. Recurrent severe pancreatitis, peptic ulcer disease, and anemia occur with greater frequency in patients with malignant disease than in those with benign PHPT. Parathyroid carcinoma shares many clinical features with acute PHPT, sometimes called "parathyroid crisis" (marked elevations of serum calcium and PTH) and the diagnosis of parathyroid cancer should thus always be considered in these patients [55]. Although the distinction between the two entities is not possible preoperatively, it is important to bear in mind the diagnosis of malignancy because the surgical approach differs.

In patients with severe PHPT, but not in parathyroid crisis, the distinction between benign or malignant disease may be even more difficult on clinical grounds, because severe hypercalcemia, renal, and bone involvement may occur, and the latter manifestations may present at the same time. However, it is preferable to have a high index of suspicion for parathyroid carcinoma when these features are present than to miss the opportunity for surgical cure (more extended surgery) by failing to consider it in the differential diagnosis.

Pathologic Features

Carcinomas are mostly irregular and hard, adherent to the surrounding soft tissues of the neck or the thyroid gland. They are usually over 3 cm in diameter and weight between 2 and 10 g [2, 4, 56]. On cross-section, carcinomas are gray-white and areas of necrosis may be present as yellow foci.

In 1973 Shanz and Castleman recognized a set of features of parathyroid carcinoma [57]. These features include uniform sheets of cells (usually chief) arranged in a lobular pattern and separated by dense trabeculae, capsular or vascular invasion, and mitotic figures within the parenchymal cells, which must be differentiated from endothelial cell mitoses. Unfortunately, none of these features is pathognomonic of parathyroid malignancy, since they can also be found in a subset of parathyroid adenomas, which are referred as "atypical adenomas" [2]. Thus, as mentioned before, the distinction between benign and malignant parathyroid tumors cannot be definitively established by histology, unless there is evidence of invasion of extratumoral vessels, perineural spaces, or surrounding tissues (thyroid gland and other adjacent structures). However, it is noteworthy that capsular and vascular invasion are present in approximately 60 and 10–15% of cases, respectively [2]. Thus, a substantial proportion of unequivocal carcinoma lacks those features which are pathognomonic of malignancy. On the other hand, the diagnosis of parathyroid

cancer is definitely established by the presence of local or distant metastases [1, 3], features which identify a late stage of the disease with a poor prognosis and low cure rate.

To further improve the accuracy of the diagnosis of parathyroid carcinoma several other histological techniques have been investigated. Electron microscopy of parathyroid cancer tissue reveals nuclear and mitochondrial alterations, nuclear diameter and DNA content greater than in adenoma, and evidence of increased secretory activity, but none of these features clearly distinguish benign from malignant tumors [58–61].

In addition, immunohistochemistry has been widely used in an attempt to further improve the differential diagnosis between benign and malignant parathyroid tumors. One approach has involved the use of proliferation markers. Increased labeling of cell cycle-associated antigens (Ki-67, cyclin D1) has been shown in parathyroid carcinoma as compared to adenoma [62–66], but the overlap among these tumor types has limited the utility of this approach, particularly in equivocal cases. Decreased expression of p27, an inhibitor of cyclin-dependent kinase, has been demonstrated in carcinomas and the association between low p27 and high Ki-67 labeling has been suggested to increase the likelihood of malignancy [67]. Recently abnormal Galectine-3 expression has been reported in parathyroid carcinoma [68]. Loss/altered expression of the calcium-sensing receptor (CASR) is present in a subset of parathyroid carcinoma [69].

Following the demonstration that the *HRPT2* gene is involved in the pathogenesis of sporadic parathyroid carcinoma, several studies have

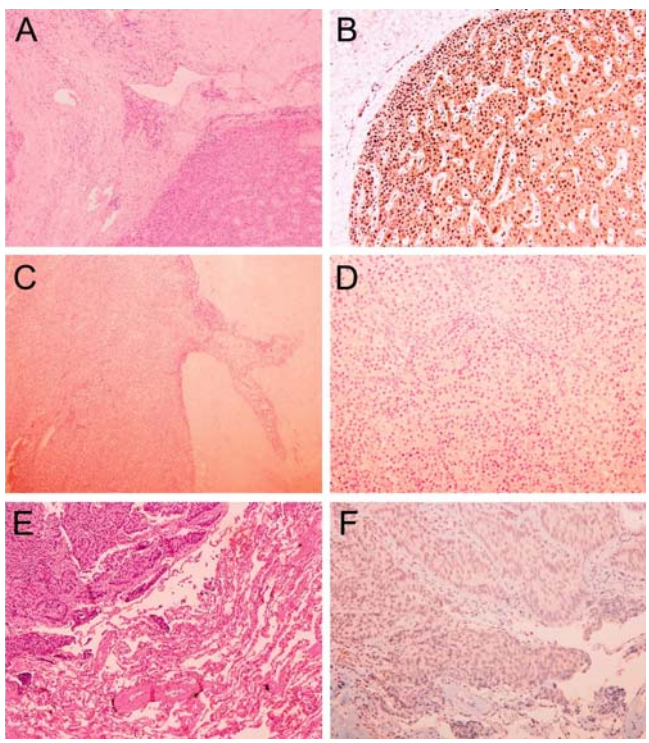

Fig. 23.2. Pathology (*left panels*) and parafibromin immunohistochemistry (*right panels*) of parathyroid tumors and lung metastasis. *Upper panels*: Parathyroid carcinoma. (**A**) Oncocytic cells arranged in trabeculae, fibrous bands, (hematoxylin and eosin, ×100); (**B**) the neoplastic cells were completely negative for parafibromin (×200). *Middle panels*: Lung metastasis of a patient with parathyroid carcinoma. (**C**) A solid trabecular neoplastic lesion and adjacent normal lung parenchyma (hematoxylin and eosin, ×100); (**D**) The tumor cells showed a diffuse loss of parafibromin staining (×200). *Lower panels*: Atypical parathyroid adenoma. (**E**) Trabecular pattern with fibrous vascular pseudo invasion (hematoxylin and eosin, ×100); (**F**) Diffuse nuclear immunoreactivity of parathyroid cells (×200).

Table 23.2. Diagnostic value (%) of *HRPT2* gene abnormalities for differentiating parathyroid carcinomas from adenomas (including atypical adenomas)

	Loss of parafibromin immunostaining	HRPT2 mutation	LOH
Sensitivity (95% CI)	100 (68–100)	82 (48–97)	64 (32–88)
Specificity (95% CI)	88 (69–97)	96 (78–100)	96 (78–100)
Positive predictive value at 0.5% prevalence (95% CI)	4 (0–11)	10 (1–19)	8 (0–16)
Negative predictive value at 0.5% prevalence (95% CI)	100 (100–100)	100 (99–100)	100 (98–100)

Modified from Cetani et al. [12]

been performed to evaluate whether immunostaining of the parafibromin, the gene product, might have some diagnostic utility. A loss (total or focal) of staining has been reported in the large majority of parathyroid carcinomas and very rarely in adenomas [10–13] (Fig. 23.2), but limited data are currently available in equivocal cases, where this would have a major diagnostic value. In this regard, our data indicate that negative parafibromin staining combined with *HRPT2* mutations is strongly associated with parathyroid cancer. Therefore, in our opinion, all suspected parathyroid tumors should be evaluated for abnormalities of *HRPT2*/parafibromin.

The high rate of *HRPT2* abnormalities in carcinomas suggests the potential diagnostic utility of *HRPT2* mutation status and/or parafibromin staining, particularly in cases with equivocal initial histology (see below). The diagnostic potential of such a test hinges on the high frequency of abnormalities in carcinomas as opposed to the low frequency in adenomas. The clinical utility of a diagnostic test depends on the prevalence of the disease in a given population (Table 23.2). The prevalence of PHPT ranges between 1 and 5‰ in the general population, but may be as high as 2% in postmenopausal women [1, 70]. It is due to a benign, single adenoma in 80% of cases and very rarely to parathyroid carcinoma (<1%). Thus, even a low detection rate of *HRPT2* abnormalities in parathyroid adenomas could adversely impact the diagnostic specificity and to a greater extent the positive predictive value of *HRPT2* abnormalities in the differential diagnosis between parathyroid adenomas and carcinomas.

Natural History

Parathyroid carcinoma typically runs an indolent, albeit progressive, course because the tumor has a rather low malignant potential. At initial presentation, very few patients have the involvement of regional lymph nodes (<5%) or distant sites (<2%) [1, 3].

It recurs locally and spreads to contiguous structures in the neck. Metastases occur late in the course of the disease with spread to cervical nodes (30%) and lung (40%), and, less frequently, to liver (10%). Rarely distant metastases occur in bone, pleura, pericardium, and pancreas. Many patients with the diagnosis of parathyroid cancer are alive 10 years afterwards.

Management and Prognosis

Surgery

Surgery is the only effective treatment for parathyroid carcinoma and consists of complete resection of the primary lesion at the time of initial operation when extensive local invasion and distant metastases are less likely [1, 3, 54, 71–73]. For this reason, both preoperative suspicion and intraoperative recognition of a potential malignant lesion are of great importance. Patients with a clinical presentation suggestive of parathyroid carcinoma warrant thorough exploration of all four parathyroid glands, as parathyroid carcinoma has been report to coexist with benign adenomas or hyperplasia [20]. The most effective therapy is en bloc resection [74]. The standard en bloc resection consists of the removal of the parathyroid tumor

along with the ipsilateral thyroid lobe. Holmes et al. [75] suggested a more aggressive approach including ipsilateral thyroidectomy and isthmusectomy, skeletonization of the trachea, excision of the neighboring muscles, and removal of the recurrent laryngeal nerve, if involved. Care should be taken during dissection to avoid rupture of the capsule, as cell spillage is associated with multifocal recurrences and persistent hypercalcemia. Tracheoesophageal, paratracheal, and upper mediastinal lymph nodes should be excised, but an extensive lateral neck dissection is indicated only when there is spread to the lateral cervical nodes.

When the diagnosis is made in the early postoperative period on the basis of pathology, as most usually happens, the management plan becomes more complex. A further element of complexity relates to the fact that some malignant lesions lack those features which are virtually diagnostic of malignancy. If the macroscopic characteristics of the tumor were typical of a parathyroid carcinoma and the pathology showed extensive vascular or capsular invasion or if hypercalcemia persists, reexploration of the neck is indicated. The structures surrounding the tumor should be excised as described above. When the telling histological features are absent, the patient is normocalcemic and the diagnosis is only based on the pathology, immediate reoperation is not indicated, as a simple complete resection of the tumors may be curative. Such patients should be monitored closely with serum calcium and PTH level measurements.

Following parathyroidectomy patients may experience the hungry bone syndrome, which results in symptomatic hypocalcemia due to the rapid deposition of calcium and phosphorus in the bones [1, 3]. Hypocalcemia may be severe and require administration of intravenous calcium. Supplements of calcium and calcitriol should be given in order to maintain normal levels of the serum calcium. When recovery of the normal parathyroid glands occurs, generally after several weeks, the vigorous replenishment of calcium can be stopped. Thereafter, serum calcium and PTH levels should be monitored every 3 months.

Despite a potentially curative resection, parathyroid carcinoma has a recurrence rate of more than 50%. Most recurrences occur 2–3 years after the initial operation, but this period is variable and a prolonged disease-free interval of as long as 23 years has been reported [1, 3, 73]. Parathyroid carcinoma metastasizes through both lymphatic and hematogenous routes. The regional lymph nodes are common sites of metastases (30%), and distant metastases most frequently involve lungs and bones, followed by the liver and other visceral organs [1–3, 13].

When a recurrence of parathyroid carcinoma is suspected, a thorough physical examination of the patients should be performed, with particular attention to the neck, since recurrences most often occur at the original site, and may be appreciated by simple palpation. Imaging studies should be performed in all patients before reoperation. Neck ultrasonography is fast and can detect cervical recurrences. Technetium 99m-sestamibi can visualize local recurrences and distant metastases [76]. It can be also used for the intraoperative localization of abnormal parathyroid tissues [77]. Octreotide scanning has also been used [unpublished data]. Computerized tomography and magnetic resonance imaging are useful adjuncts to ultrasonography in the evaluation of the neck and are superior for detection of metastases in the chest or abdomen. If noninvasive examinations are negative, arteriography and selective venous sampling for PTH measurement may be useful. Fine-needle aspiration and measurement of PTH in the eluate [78] should be used with caution, if at all, to avoid seeding the needle track with deposit of malignant cells [79].

The management of recurrent or metastatic parathyroid carcinoma is primarily surgical [1, 3, 54, 71–75]. Recurrences in the neck should be treated with wide resections, including the regional lymph nodes and other involved structures. Distant metastases should also be excised, if possible. Even a small tumor may produce sufficient amount of PTH to cause hypercalcemia. Although resection of single metastasis or other foci of malignant tissue is rarely curative, its removal may result in periods of normocalcemia ranging from months to years [3]. Decreasing tumor mass may also render the patient's hypercalcemia more amenable to medical treatment.

Chemotherapy

The rarity of parathyroid cancer precludes any prospective study to examine the effects of chemotherapy, and thus, most knowledge on this

matter comes from case reports. It is with these limitations in mind that the following comments should be interpreted. Several regimens have been attempted, using nitrogen mustard, vincristine, cyclophosphamide, actinomycin D, and adriamycin alone or in combination with cyclophosphamide and 5-fluorouracil, but none of them proved to be effective [51, 80]. Currently, there is no role for chemotherapy in the management of patients with parathyroid carcinoma.

Radiotherapy

With the exception of Wynne et al. [51], who reported an apparent cure (10 year) in a patient with tumor invasion of trachea, radiation therapy has little, if any, effect in the management of invasive parathyroid cancer [73]. Recent reports have suggested the use of irradiation as adjuvant therapy. The Mayo Clinic has reported a disease-free survival at a median follow-up period of 60 months in four patients who received postoperative radiotherapy [81]. The MD Anderson Cancer Center experience suggests a lower local recurrence rate if adjuvant radiation was given after surgery, independent of the type of operation and the disease stage [82, 83].

Management of Hypercalcemia

When parathyroid carcinoma has become widely metastatic and surgical options are exhausted, clinical management turns to controlling the hypercalcemia.

Hypercalcemia of parathyroid carcinoma is treated in the same way as hypercalcemia due to any other cause is treated [84]. Saline infusion and loop diuretics are often used, but, in the majority of cases drugs that inhibit bone resorption are needed. Potent intravenous bisphosphonates (pamidronate and zoledronate) may transiently control hypercalcemia, but patients frequently become refractory to them. Plicamycin, another inhibitor of bone resorption, is effective, but the response is transient, and repeated courses may be associated with toxicity. Gallium nitrate inhibits bone resorption by preventing dissolution of hydroxyapatite crystals. It is an effective hypocalcemic drug, but its use is limited by nephrotoxicity. Calcitonin also reduces transiently serum calcium in patients with parathyroid carcinoma. WR-2721 is a hypocalcemic agent that acts by inhibiting PTH secretion and bone resorption [85]. Severe toxicity limits its use. Octreotide, the long-acting somatostatin analogue, has also been reported to inhibit PTH secretion in two cases of metastatic parathyroid carcinoma [86, 87].

Another approach is to target the parathyroid CASR. Calcimimetics, allosteric modulators of the CASR, directly reduce parathyroid cell hormone secretion by binding to sites that increase the receptors affinity for calcium. Thus, sensitivity to extracellular calcium is enhanced [88]. A first-generation calcimimetic, R-568, was used for 2 years in a patient with metastatic parathyroid cancer with controlled hypercalcemia [89]. R-568 has been replaced by cinacalcet, a more potent second-generation agent with a longer half-life. In benign PHPT, cinacalcet normalized serum calcium and reduced PTH concentrations for up to 3 years [90]. Recently, we published the results of a multicentric investigation of cinacalcet in 29 patients with inoperable parathyroid carcinoma [91].The primary endpoint of the study was the proportion of patients experiencing a $\geq$1 mg/dl reduction in serum calcium from baseline at the end of the titration phase. Secondary endpoints included changes from baseline in serum calcium, plasma PTH, bone turnover markers, and health-related quality of life variables. Duration of treatment ranged from 1 to 1051 days (mean 328 ± 306 days). Cinacalcet effectively reduced hypercalcemia in about two thirds of patients with inoperable parathyroid carcinoma. This drug, may, therefore, represent an important new treatment option for these patients.

Another novel and promising approach is anti-PTH immunotherapy [92]. A positive response has been observed in a patient with metastatic parathyroid carcinoma immunized with a mixture of human and bovine PTH peptides [93]. This treatment was followed by a rapid control of hypercalcemia and improvement in clinical condition, decrease of the size of lung metastases, without relevant adverse effects. Recently, a monoclonal antibody to PTH has been used for the treatment of parathyroid carcinoma [94]. Dendritic cell immunotherapy may also be applicable to induce a T-cell immune response [95].

Prognosis

The prognosis of parathyroid carcinoma is quite variable. No one characteristic correlates with outcome. The best prognosis depends upon early recognition and complete excision of the tumor at initial surgery. The mean time to recurrence is usually 3 years, although intervals of up to 20 years have been reported. When the tumor recurs, complete cure is unlikely, although prolonged survival is still common with palliative surgery. Five-year survival rates vary from 40 to 86%. The National Cancer Database survey reported a 10-year survival of approximately 49% [14] and the MD Andersen Cancer Center reported survival rates of 85 and 77% at 5 and 10 years, respectively [82]. The National Surveillance, Epidemiology, and End Results database recently reported a 10-year survival of 67.8% [96].

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Section III
Adrenal

24

Adrenal Embryology, Anatomy, and Physiology

Donal Shanahan and Thomas William Jay Lennard

Embryology

The paired adrenal (suprarenal) glands are flattened retroperitoneal endocrine glands closely applied to the medial aspect of the superior pole of each kidney. The internal structure of these pale yellow glands are incongruous in that the adrenal gland is composed of two discrete parts, namely an outer cortex enveloping a central medulla. The adrenal cortex and medulla contain distinct endocrine tissues that secrete different hormones and are regulated by separate control systems. As such, the parts of the adrenal gland have different embryological origins, in that the cortex is derived from coelomic (body cavity) epithelium whereas the medulla is ectodermal in origin arising from the neural crest (Fig. 24.1).

In the sixth week of intrauterine life the adrenal fetal cortex develops from the body cavity epithelium. The fetal cortex is thick and spherical in shape, a second group of cells surround the fetal cortex and forms the definitive cortex. The outer part of the fetal cortex gives rise to the zona reticularis whereas the definitive cortex differentiates into zona glomerulosa and zona fasciculate (Fig. 24.2). The inner part of the fetal cortex persists throughout intrauterine life but it degenerates shortly after birth.

The neural crest is the name given to the band of cells at the outermost edges of the neural band. Migration of neural crest cells leads to the formation of the dorsal root ganglia and sympathetic ganglia. Neural crest cells accumulate in a mass that will become the adrenal medulla on either side of the body cavity (Figs. 24.1 and 24.2). Relative to body weight the fetal adrenal glands (Fig. 24.3) are 10–20 times larger than the adult adrenal gland [1] (Figs. 24.4 and 24.5).

Shortly after formation of the adrenal cortex, neural crest cells migrate into the center of this accumulation of cells to develop into the adrenal medulla. The cortex engulfs the medulla until the medulla is completely enclosed. During intrauterine life two cortical layers surround the medulla, first the zona glomerulus and then the zona fasciculate, a final layer the zona reticularis is formed after birth at around 3 years of age (Fig. 24.6). Therefore, the formation of the adrenal gland is not completed until the end of three years of age.

During fetal development the migration of adrenocortical and medullary cells can result in accessory or ectopic tissue. Adrenocortical tissue has been found around the kidney, along gonadal vessels and uterus. This tissue can be responsible for the recurrence of Cushings post adrenalectomy secondary to excess ACTH secretion. Adrenal medullary cells can persist anywhere along the path of neural cell migration and that explains the occurrence of extra adrenal pheochromocytoma.

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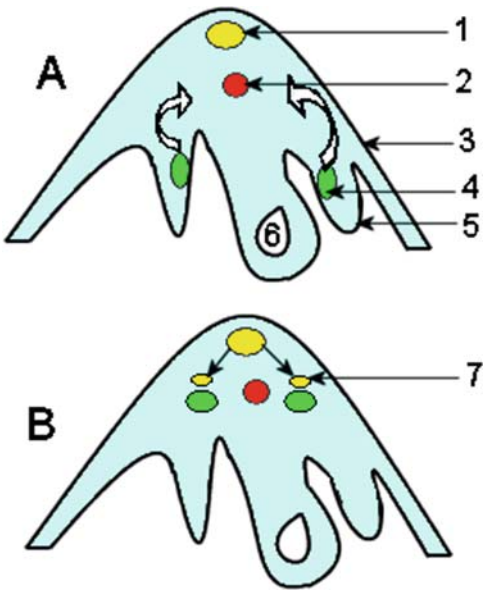

Fig. 24.1. Development of the adrenal gland. Transverse section of developing fetal abdomen. Adrenal cortex develops before medulla. (**A**) At 6 weeks of development adrenal cortex cells migrate from coelomic epithelium into body cavity. (**B**) At 7 weeks of development neural crest cells migrate into adrenal cortex. 1 = Spinal cord, 2 = Aorta, 3 = Surface ectoderm, 4 = Adrenal cortex, 5 = Coelomic epithelium, 6 = Hindgut, and 7 = Adrenal medulla.

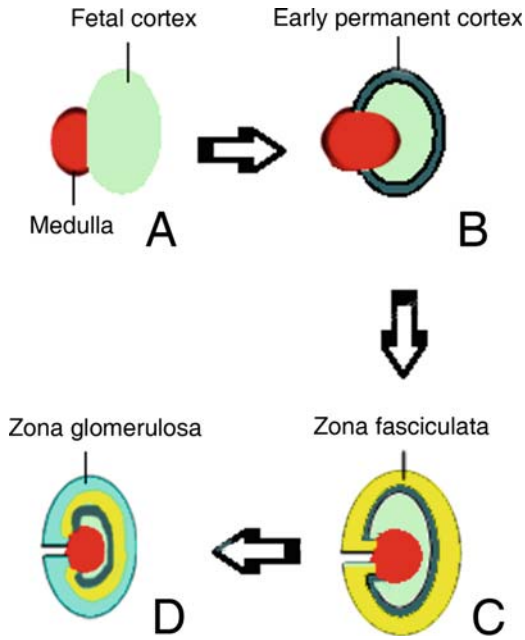

Fig. 24.2. Development of the adrenal gland. (**A**) 7 weeks; (**B**) 8 weeks; (**C**) 20 weeks; (**D**) newborn.

Anatomy

Due to the large size and position of the liver, the right adrenal gland and kidney lie inferior to the left adrenal gland and kidney. Therefore, the upper pole of the left kidney rises to the level of the eleventh rib but the right kidney is slightly lower [2]. In external appearance the right and left adrenal glands are dissimilar in that the former is pyramidal in shape whereas the left adrenal gland is larger and lunate in shape.

Anterior to the right adrenal gland is part of the right lobe of the liver and the inferior vena cava. Anterior to the left adrenal gland is part of the body and pylorus of the stomach, pancreas, and sometimes the spleen. Posterior to both adrenal glands is the diaphragm laterally and the psoas fascia covering the psoas major muscles medially. Lateral to the adrenal gland is the superior pole of the kidney.

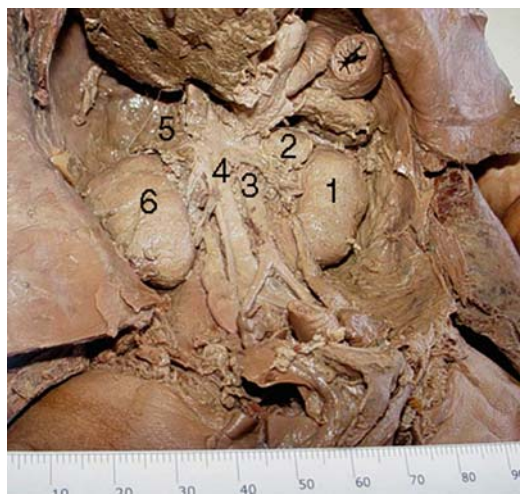

Fig. 24.3. White female, premature, stillborn. Length, 43 cm; weight, 2.2 kg. 1 = Left kidney, 2 = Left adrenal gland, 3 = Abdominal aorta, 4 = Inferior vena cava, 5 = Right adrenal gland, 6 = Left kidney. (Courtesy of Mr. Albert Van Schoor, Department of Anatomy, School of Medicine, Faculty of Health Sciences, University of Pretoria, South Africa).

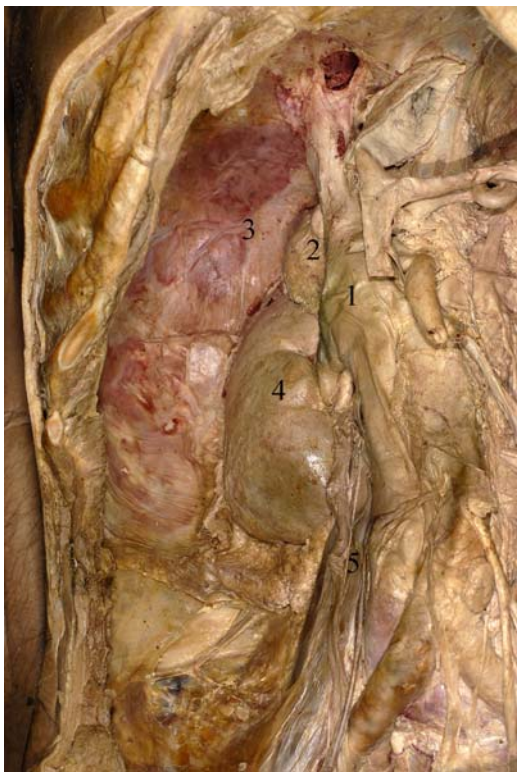

Fig. 24.4. Relations of the right adrenal gland. 1 = Inferior vena cava, 2 = Right adrenal gland, 3 = Right dome of diaphragm, 4 = Right kidney, 5 = Right psoas major muscle. (Photographed by Mr. Frank Addison, Walton Library, Newcastle University, England).

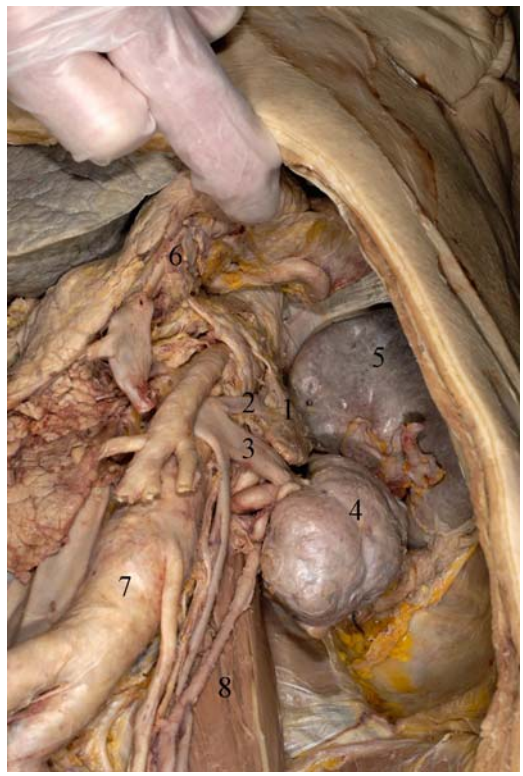

Fig. 24.5. Relations of the left adrenal gland. 1 = Left adrenal gland, 2 = Left adrenal vein, 3 = Left renal vein, 4 = Left kidney, 5 = Spleen, 6 = Body of pancreas, 7 = Abdominal aorta, 8 = Left psoas major muscle. (Photographed by Mr. Frank Addison).

Superior to the right adrenal gland is the liver and superior to the left adrenal gland is the left dome of the diaphragm and spleen (Figs. 24.4 and 24.5).

The adrenal glands like other endocrine glands receive a rich blood supply. The blood supply to the adrenal glands arises from the inferior phrenic arteries, aorta, and renal arteries (Figs. 24.4 and 24.5). The superior adrenal artery arises from the inferior phrenic artery, the middle adrenal artery arises directly from the abdominal aorta, and the inferior adrenal artery arises from the renal artery (Fig. 24.5). These three groups of arteries form a plexus within the capsule of the adrenal gland. This capsular plexus gives rise to small arteries that descend through the cortex into the medulla where they branch into an elaborate network of dilated capillaries surrounding the medullary secretory cells (Fig. 24.6). The capsular plexus also supplies the cortex by forming a network of capillary sinusoids.

The capillary sinusoids descend between the secretary cells of the cortex to drain at the corticomedullary junction into small veins that then drain into the central vein of the medulla. The medullary capillaries also drain into the central vein of the medulla [3]. Therefore, the venous return from the adrenal glands consists of a single vein that on the right drains directly into the inferior vena cava and on the left drains into the left renal vein (Fig. 24.5).

Lymphatic drainage from the cortex and medulla of adrenal glands is directly into the

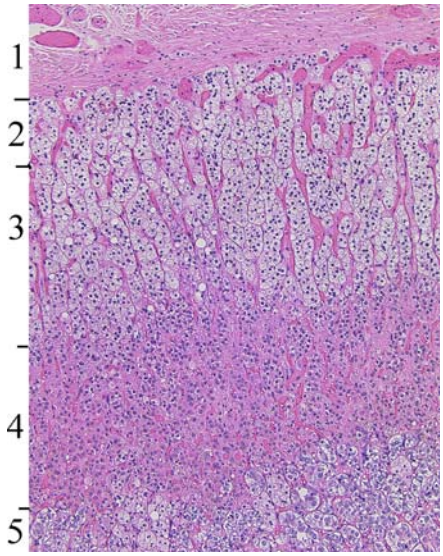

Fig. 24.6. H&E stain of adrenal gland, X 200. 1 = Connective tissue capsule. 2 = Zona glomerulosa. 3 = Zona fasciculate. 4 = Zona reticularis. 5 = Medulla. (Courtesy of Dr. Sarah Johnson, Royal Victoria Infirmary, Newcastle Upon Tyne, England; we are grateful to Mr Harry Elliot, School of Applied Sciences, Northumbria University, England for assisting with this figure).

para-aortic lymph nodes. Lymph from the paraortic lymph nodes drain into the cisterna chyli and then via the thoracic duct into the confluence of the left internal jugular vein and left subclavian vein.

The adrenal nerve plexus lies medial to the gland and contains mostly preganglionic sympathetic fibers from the lower thoracic spinal segments, this input travels via the coeliac plexus and greater splanchnic nerve to the adrenal nerve plexus. The neuroendocrine cells within the adrenal medulla are chromaffin cells which are modified sympathetic ganglion cells that receive direct synaptic contacts from preganglionic fibers from the eleventh and twelfth thoracic segments. Chromaffin cells secrete adrenaline, noradrenaline, and enkephalin into the capillary bed around the individual cells and as such play an important role in the fight or flight response. These sympathetic fibers synapse with the large medullary chromaffin cells which can be considered analogous to postganglionic sympathetic neurons [4].

Adrenal Physiology

Output from the adrenal gland from the two functional components of the gland, the cortex, and the medulla is very distinct and different. The outer cortex represents 85% of the gland and the medulla in the center 15%. The cortex has three zones, an outer zone, the zona glomerulosa which secretes aldosterone and the zona fasciculata and the zona reticularis which are effectively a functional unit producing cortisol and small amounts of sex steroids.

Aldosterone

Aldosterone is released from the zona glomerulosa in response to a fall in blood volume or an increase in serum potassium. Its function is to contribute to blood pressure homeostasis. Aldosterone secretion is subject to circadian variation. Sympathetic nerves attached to the adrenal gland, acting via BARO receptors detect a fall in blood pressure, and also induce secretion of aldosterone. In the kidney, the juxtaglomerular apparatus contains cells which synthesize renin, a hormone which is secreted directly as a result of sympathetic nerve stimulation and also in response to a fall in renal artery perfusion pressure. Renin induces the conversion of angiotensinogen to angiotensin I, which in turn is converted to angiotensin II via the angiotensin-converting enzyme system, largely in the lung. Angiotensin II has a direct effect on the secretion of aldosterone (Fig. 24.7).

Cortisol

Cortisol is secreted from the zona fasciculata, principally under the control of ACTH. Multiple cofactors, however, also influence cortisol secretion including vasopressin and physical and emotional stress. ACTH is secreted from the anterior pituitary in response to cortisol-releasing factor produced in the hypothalamus. The neurons in the hypothalamus secrete small bursts of CRF into the pituitary portal circulation which in turn stimulates the release of ACTH, a 39-amino acid protein.

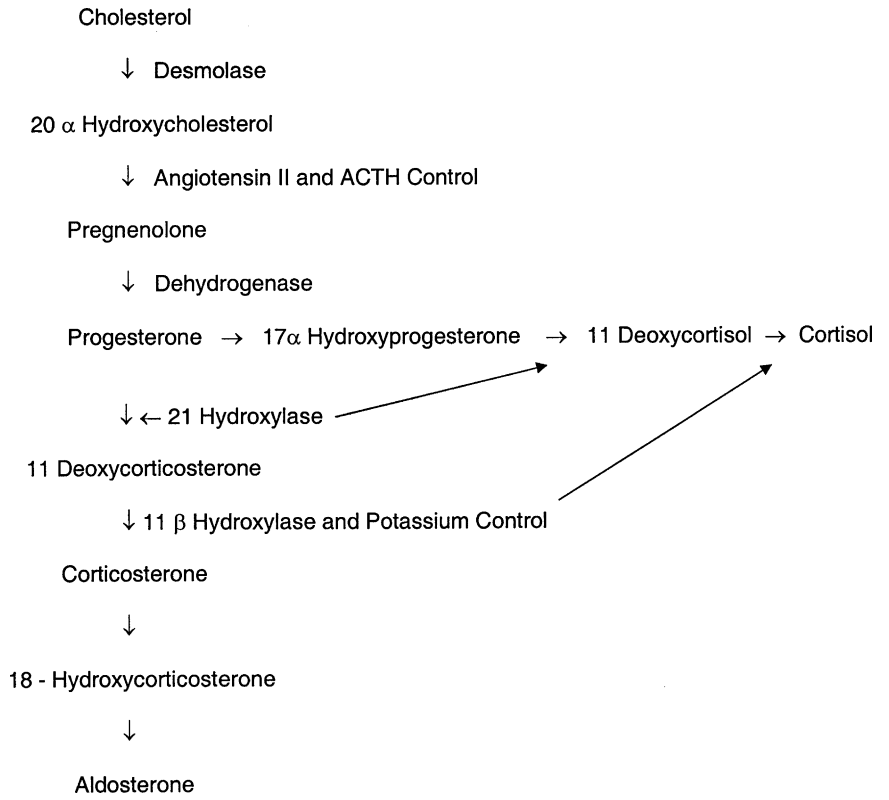

Fig. 24.7. Pathway for the synthesis of aldosterone and cortisol.

This is subject to circadian variation. ACTH acts directly on the adrenal gland to produce cortisol. Cortisol is largely secreted to order and is not stored and once in the circulation 95% of it is bound to protein. The active component is free and unbound and only 5% of the total cortisol secreted. There is a negative feedback loop which feeds back to the hypothalamus and pituitary to regulate and control the secretion of cortisol. The plasma half-life of cortisol is 80–120 min. Its function is part of the stress response, mobilizing substrate from stores, reducing inflammation, and raising blood pressure.

Sex Steroids

In the zona reticularis sex steroids are produced, for example, dehydroepiandrosterone (DHEA). These small amounts of sex steroid are of relatively little physiological significance except for two situations. Firstly, in the postmenopausal female when the ovaries cease to produce significant hormones the adrenal gland then becomes the main source of sex steroids. This can be exploited, for example, in the treatment of postmenopausal women in breast cancer [5–7]. Inhibition of the enzymes (aromatase), which convert adrenal sex steroids into estrogen, largely in fat, can be inhibited with drugs. The second incidence where adrenal sex steroids become relevant is when there are defects in the synthesis of enzymes (most commonly 21 and 11 hydroxylase) responsible for the conversion of sex steroids in the adrenal gland. In these circumstances at different levels in the sex steroid pathway (Fig. 24.7) there can be a build up of hormonally active substrate which can on occasion lead to ambiguous gender in an infant. Associated with this there is often significant adrenal hyperplasia [5–7].

The mechanisms of action of adrenal cortical steroids are all largely similar. The hormones

are fat soluble and they enter cells to bind to a specific, usually nuclear, receptor. The ligand receptor complex binds to DNA and induces protein synthesis. Most hormones are metabolized in the liver to water-soluble products which are then excreted in the urine.

Hormones and their metabolites can readily be measured either directly in the plasma or in the urine and in addition dynamic tests of the negative feedback systems can be carried out to assess the integrity and functionality of the hypothalamic pituitary adrenal axis. Examples of this include the dexamethasone suppression test where exogenous corticosteroid (dexamethasone) is given to assess the negative feedback and suppression of ACTH production. Similarly, synthetic ACTH can be given to assess the resultant expected cortisol secretion by the cortex.

The Adrenal Medulla

This small central core of the adrenal gland produces catecholamines. These are synthesized in the medulla from tyrosine (Fig. 24.8). The conversion from dopamine to noradrenaline and adrenaline occurs in a roughly 20%/80% split, the majority being adrenaline. The secretion of catecholamines is under direct control from the sympathetic nervous system and several stimuli will induce catecholamine secretion including acidosis, hypovolemia, hypoglycemia, hypoxia, cold, and fright. In essence, this is a response to stress of any type. Cortisol from the adrenal cortex also influences the conversion of noradrenaline to adrenaline. The enzyme phenylethanolamine-N-methyltransferase converts norepinephrine to epinephrine in the adrenal gland, but is lacking in extra adrenal medullary tissue. Extra adrenal pheochromocytomas therefore predominantly secrete norepinephrine. Catecholamines are broken down by the enzyme monoamine oxidase and are excreted in the urine where they can be readily measured both as a breakdown product and as a free hormone. Catecholamine presence in the circulation is short lived so the measuring of plasma catecholamines is possible but difficult and expensive due to their rapid breakdown in plasma.

Catecholamines have a large number of physiological effects, including rising heart rate and blood pressure, as well as cardiac output, increasing peripheral resistance, excitation of the central nervous system, and sweating. Catecholamines also induce the breakdown of fat, glycogen, and protein to produce substrate for the "fight or flight" response. The actions of catecholamines are mediated through α and β receptors [5–7].

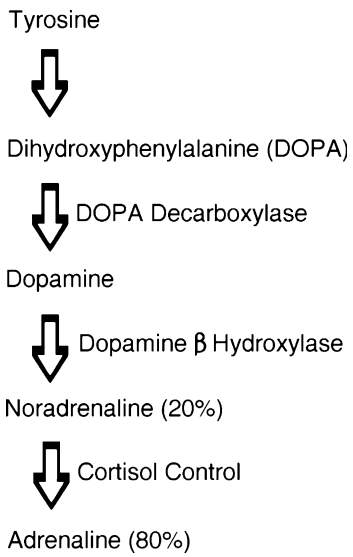

Fig. 24.8. Pathway for the synthesis of catecholamines.

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25

Adrenal Imaging

Elizabeth G. Grubbs, Rodolfo F. Nuñez, Revathy B. Iyer and Nancy D. Perrier

Introduction

Adrenal imaging has historically been used for localization and operative planning in patients with biochemical evidence of adrenal disease. However, with advances in imaging techniques, it is now common for incidental adrenal masses to be detected on abdominal imaging that was performed for "nonendocrine" disease. Adrenal imaging now has a role in determining the nature – functioning or nonfunctioning, benign or malignant – of these incidentally discovered adrenal lesions. In this chapter, we review adrenal imaging modalities and discuss their indications and limitations.

Adrenal Anatomy

A precise understanding of the adrenal anatomy is necessary to interpret imaging studies of these structures within the retroperitoneum. Knowledge of the adrenal glands' blood supply and relationship to other organs is critical to tumor localization and operative planning. Each adrenal gland is composed of two physiologically distinct parts: the cortex and the medulla. Histologically, both the medulla and the cortex have a high lipid content; thus, they cannot be differentiated by computed tomography (CT) or magnetic resonance imaging (MRI).

In the medical literature, most measurements of adrenal size refer to the body of the gland. However, given the predominance of cortical tissue within the limbs of the gland, measurements of these portions are important as well. The maximum width of the body measured perpendicular to the long axis, at the junction of the adrenal body and the limbs is 0.79 cm for the left adrenal and 0.6 cm for the right adrenal. The thickness of the left adrenal limbs (0.13–0.52 cm) is slightly greater than that of the right (0.14–0.49 cm). A normal adrenal limb should not measure more than 0.5 cm in length [1].

Computed Tomography

CT Overview

CT continues to be the initial imaging modality of choice for the diagnosis and characterization of adrenal tumors. High-quality CT with sections obtained through the abdomen and pelvis has the advantages of moderate cost and high sensitivity; the sensitivity of CT for detecting adrenal lesions is in fact 93–100% [2, 3, 4].

The ideal protocol for detecting and characterizing adrenal lesions includes noncontrast-enhanced CT followed by intravenous administration of iodinated contrast material and then immediate and delayed contrast-enhanced CT – all obtained with 2- to 5-mm thick collimation. With high-quality

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multidetector (multislice) CT, 95% of adrenal masses larger than 6–8 mm can routinely be detected.

Noncontrast-enhanced images and delayed contrast-enhanced images can be used to distinguish benign adrenocortical adenomas from adrenocortical carcinoma (ACC), pheochromocytoma, and metastatic disease. Using helical nonenhanced CT imaging with delayed contrast-enhanced imaging at 1 and 10 min after contrast injection, benign adenomas typically have rapid washout of the contrast material and pheochromocytomas have slower washout [5]. In fact, the percentage of contrast enhancement loss, both absolute and relative, at 10 min is quite sensitive for characterizing benign tumors. In a study by Pena et al., 99 of 101 lesions were correctly characterized as benign or malignant with a relative percentage washout threshold of 50% on delayed scans; benign lesions demonstrated more than 50% washout, and malignant lesions, less than 50% washout [6].

CT Characteristics of Benign Adenomas

Benign adrenocortical adenomas typically have a high lipid content. When imaged using noncontrast-enhanced CT, the high lipid content imparts low attenuation values, measured in Hounsfield units (HU). An attenuation of >1,000 HU is usual for bony structures, 1,000 HU for air, 0 HU for water, and <0 HU for fat. Lesions with attenuation values ≤10 HU are virtually always lipid-rich benign adenomas, whereas lesions with attenuation values >30 HU are consistently nonadenomatous tumors – ACCs, metastatic lesions, or pheochromocytomas. Lesions with intermediate attenuation values (between 10 and 30 HU) may represent lipid-poor benign adenomas and therefore must be evaluated carefully based on other imaging characteristics such as contrast enhancement and washout [2, 7]. Table 25.1 summarizes the CT characteristics of benign adrenal lesions.

Table 25.1. CT Characteristics of benign adrenal lesions

Signal drop and intensity similar to liver
Low attenuation on noncontrast-enhanced CT
• –20 to 0 HU = cyst
• <10 HU = adenoma
• –50 HU = myelolipoma
Homogeneous
Smooth borders
Smooth contour
Round or oval
<4 cm in greatest diameter

CT Characteristics of ACCs

Though rare (4–12 per 1,000,000 people), ACCs have a poor prognosis. The overall 5-year survival rate is less than 50% [8]. Complete surgical resection is the only chance of cure, and the completeness of resection, tumor stage and tumor grade are important predictors of survival [9]. Most ACCs are 10–12 cm in diameter at diagnosis [9, 10]. Preoperative knowledge that a tumor is ACC is critical to plan the correct operative approach with the greatest likelihood of eradicating all local disease.

CT detects 98% of ACCs [11]. Using a cut off of >30 HU, contrast-enhanced CT has a positive predictive value of 100% and a sensitivity of 95% in determining malignant adrenal tumors [4]. ACCs often appear heterogeneous on contrast-enhanced CT because of internal necrosis; are usually large, exceeding 5 cm in diameter; are irregular, with poorly defined margins; invade the upper pole of the kidney or inferior vena cava; and have associated adjacent nodal metastasis (Table 25.2). Calcifications or cystic degeneration is seen in about 30% of ACCs. Any evidence of local invasion or nodal metastasis supports the diagnosis of ACC. CT is in fact ideally suited to image ACCs because it allows detection

Table 25.2. CT characteristics of malignant adrenal lesions

High attenuation:
• >30 HU is suspicious
• Pheochromocytoma vs adrenocortical carcinoma (>30 HU)
Heterogeneous
Irregular borders
Local/vascular invasion
Lymphadenopathy
Metastases
Large size (>6 cm)

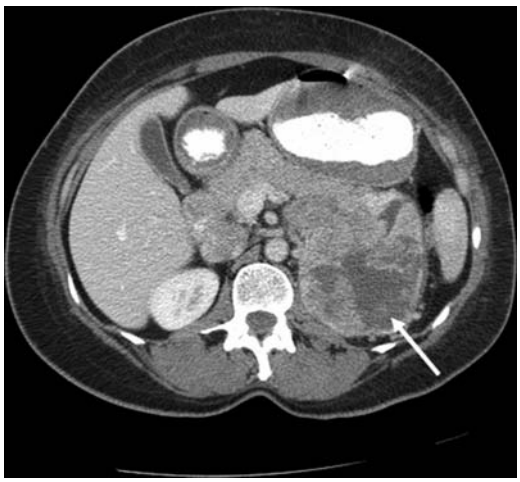

Fig. 25.1. Adrenocortical carcinoma. A 13.3-cm heterogenous mass with peripheral enhancement and central necrosis. Hounsfield units of 78 and 15 min washout of 30%.

of metastatic disease in the regional lymph nodes, liver, and lungs; enables staging of disease; and aids with surgical planning. Figure 25.1 shows the typical appearance of an ACC.

The use of intravenous contrast is important for characterizing and staging ACCs. On contrast-enhanced images, ACCs typically show peripheral enhancement of the mass with a central nonenhanced area of necrosis. The measurement of contrast washout is also valuable in distinguishing benign adrenocortical adenomas from ACCs, which have slower washout.

Size is also an important criterion when evaluating an adrenal lesion with CT. The likelihood of ACC is directly related to the size of the lesion: only 2% of adrenal lesions $\leq$4 cm are ACCs; 6% of lesions 4.1–6 cm are ACCs; and 25% of lesions $>$6 cm are ACCs. A review by Kebebew et al. of 725 ACCs in the US National Cancer Institute's Surveillance, Epidemiology, and End Results database [9] revealed a mean tumor size of 12 cm, with a range of 2–36 cm. Only 4.2% of ACCs were $<$6 cm in greatest diameter.

In a review of 182 adults evaluated and treated for an adrenal tumor at The University of Texas M. D. Anderson Cancer Center between 1971 and 2000, Barnett et al. found that only 5 (13%) of the 38 patients with ACCs had tumors $<$5 cm at diagnosis [12]. For four of these five tumors, radiographic criteria other than size suggested malignancy: heterogeneity, irregular shape, irregular margins, or hemorrhage. It is important to recognize that CT may underestimate the true histologic size of a tumor (as found in the surgical specimen) by up to 20%. In the review by Barnett et al., the mean radiographic estimate for ACCs was 9.5 cm (1.7–30 cm), but the mean pathologic measurement was 11.7 cm (3.0–30 cm). This difference was significant ($p = 0.001$).

CT Characteristics of Functioning Tumors

Pheochromocytoma

CT is accurate for detecting pheochromocytomas because of its high spatial resolution. The overall sensitivity ranges between 93 and 100% [13]. CT is less sensitive (60%) in evaluating patients with metastatic or recurrent pheochromocytoma than in those with primary tumors. Because pheochromocytomas may extend superiorly or inferiorly from an otherwise normal-appearing adrenal gland, contiguous thin sections of 5 mm are recommended when a pheochromocytoma is suspected on the basis of biochemical findings. The scans should include the diaphragm and extend below the aortic bifurcation because of the possibility of extraadrenal sites of disease. The normal contralateral adrenal gland should also be imaged. Most pheochromocytomas are rounded, homogeneous masses with an attenuation similar to or slightly less than that of liver tissue (Fig. 25.2). Pheochromocytomas occasionally show hemorrhagic, cystic, or calcified areas.

Oral contrast enhancement of the bowel with barium or an iodinated contrast agent is necessary to define the normal anatomy and prevent confusion of unpacified bowel with a soft tissue mass. Intravenous contrast enhancement increases the sensitivity of lesion detection, but there is a risk of precipitating an adrenergic crisis if appropriate alpha and beta blockade have not been instituted prior to injection of the iodinated contrast agent. It is imperative that volume expansion, hypertension control, and some degree of orthostatic hypotension be present prior to initiating the beta blockade. Phenoxybenzamine (Dibenzyline, 10 mg twice daily) for 5–7 days followed by propranolol (Inderal, 10 mg three times daily) is an acceptable medical regimen. On contrast-enhanced

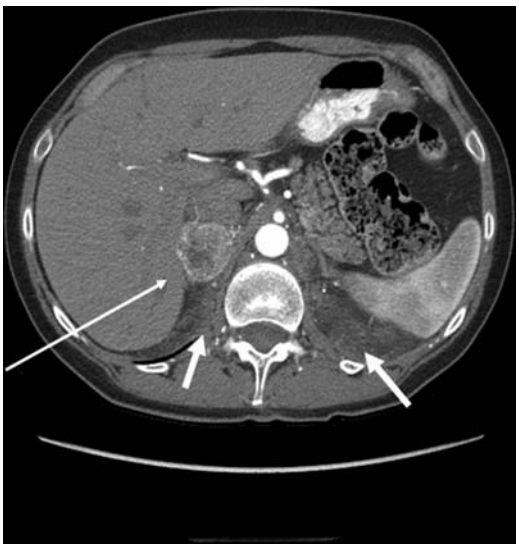

Fig. 25.2. CT of patient with pheochromocytoma (denoted by *thin arrow*) of brown fat changes (denoted by *thick arrows*) associated with pheochromocytoma.

CT scans, pheochromocytomas are irregular, and the periphery of the tumor is often more intense that the central portion.

Retroperitoneal Brown Fat

Patients with catecholamine excess may mobilize brown fat, resulting in changes in the appearance of the retroperitoneal fat. This may be seen on CT as infiltrative or vascular changes in the retroperitoneal region. The changes are diffuse and should be recognized as benign reactive changes rather than locally invasive or metastatic disease (Fig. 25.2) [14].

Aldosteronoma

The majority of patients with hyperaldosteronism have small, benign adrenal adenomas producing aldosterone. A minority (25%), however, have bilateral adrenal hyperplasia. Determination of bilateral hyperplasia is critical in the workup as patients with bilateral hyperplasia will not benefit from adrenalectomy. CT in a patient with biochemical findings suggesting hyperaldosteronism requires 0.3–0.5 cm thick contiguous slices in the adrenal region. Aldosteronomas are usually isodense and do not enhance with intravenous contrast agent administration (Fig. 25.3). Those most difficult to identify are in the apex of the adrenal. The sensitivity of CT in detecting aldosteronomas is only 85% – less than that for other functioning lesions – because of their small size [2]. Nuclear medicine studies and venous sampling are frequently necessary to confirm the type of disease (unilateral versus bilateral).

Cushing's Syndrome

Most patients with cortisol excess have exogenous intake of corticosteroids. For patients with

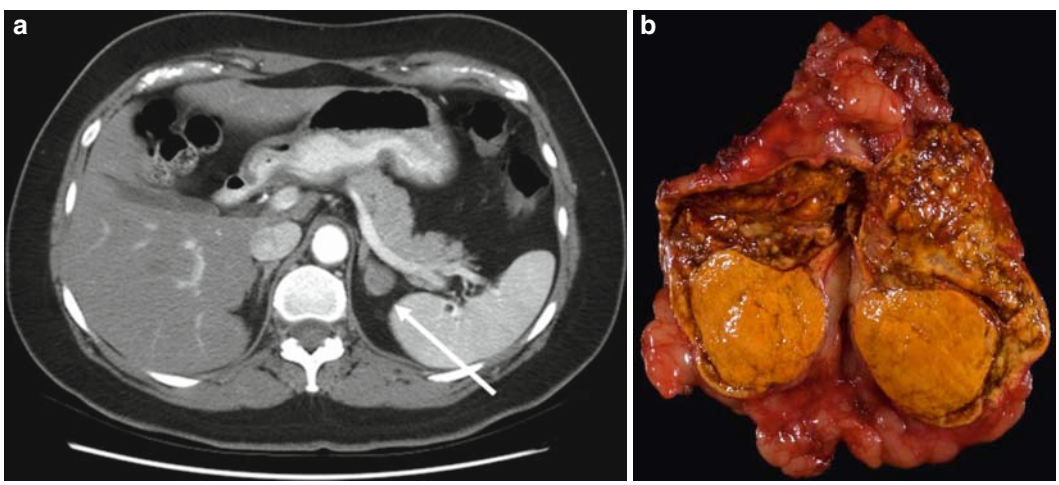

Fig. 25.3. (**a**) CT with intravenous contrast of a left-sided aldosteronoma denoted by *arrow* (**b**) corresponding pathology.

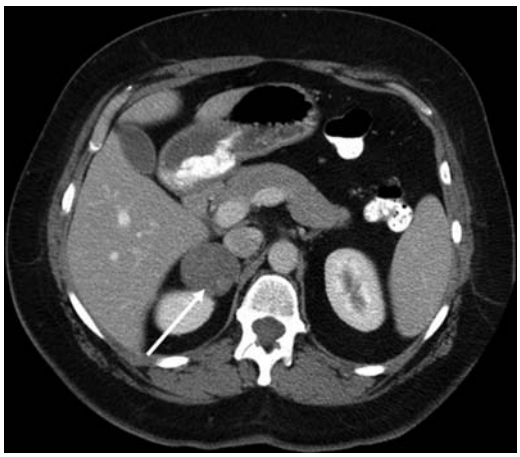

Fig. 25.4. CT of a cortisol-producing functional adenoma.

endogenous production, Cushing's disease, resulting from a pituitary tumor, accounts for the majority of cases. Only 10% of cases have a benign cortisol-secreting tumor of the adrenal gland. CT is excellent (98% sensitivity) at detecting adrenal masses causing Cushing's syndrome. Adrenal lesions capable of producing enough cortisol to become clinically apparent are usually large enough (2–5 cm) to be seen with CT. Cortisol-secreting adenomas rarely show contrast enhancement (Fig. 25.4). Visualization is aided by the regional perinephric fat that is usually present with this syndrome.

Ruling out adrenal macronodular hyperplasia is critical. In such cases, the disease is corticotropin (ACTH) dependent, and bilateral adrenal enlargement should be present without a dominant nodule. The adrenal parenchyma can be bilaterally thickened or appear normal.

CT Characteristics of Nonfunctioning Tumors

Cysts

Cystic lesions of the adrenal should be worked up thoroughly as not all of them are benign. A recent review by the Mayo Clinic revealed that 2% of ACCs present as cystic neoplasms [15]. Rim calcification may be observed on CT (Fig. 25.5).

Myelolipoma

Myelolipomas have a characteristic CT appearance because of the presence of fat and myeloid elements. As a result, a definite diagnosis can be rendered by CT. These lesions have an attenuation of <0 HU because of the fat content (Fig. 25.6). Areas of soft tissue attenuation are also seen and correspond to the myeloid tissue. Borders are usually smooth, with no evidence of invasion. Myelolipomas may be inhomogeneous and contain blood products since larger lesions may bleed.

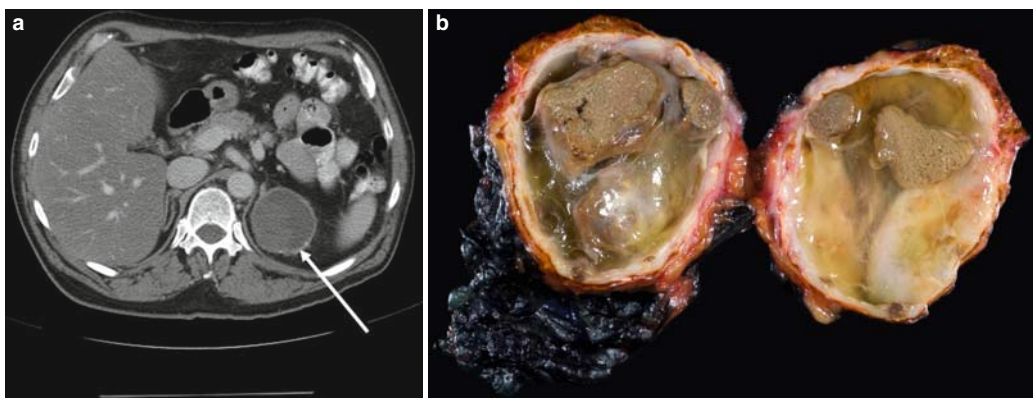

Fig. 25.5. (**a**) Calcified left adrenal cyst 6 cm in maximum diameter. (**b**) Correlating path of benign calcified left adrenal cyst.

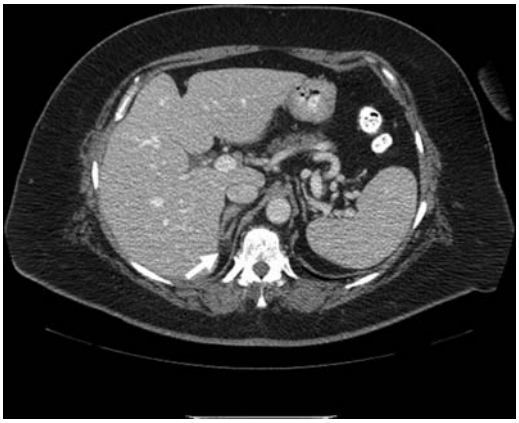

Fig. 25.6. CT of myelolipoma with −23 HU on immediate imaging. −23 HU on 15 min delayed imaging as well.

Magnetic Resonance Imaging

MRI Overview

For a number of years, CT has been the main technique for characterizing adrenal lesions because of its widespread availability and speed, particularly with multislice CT. However, MRI has proven to be of similar accuracy to CT in characterizing adrenal masses and may in fact have some advantages owing to its excellent soft tissue contrast resolution [7]. MRI also has the advantage of not exposing the patient to ionizing radiation, which is particularly important in young patients or pregnant women.

The normal-sized adrenal gland is thin and can easily be obscured on MRI by flowing blood, chemical shift misregistration, or respiration. As a result, adrenal MRI requires meticulous technique and a careful balance of high spatial resolution and appropriate signal-to-noise ratio [7]. The spatial resolution of MRI is adequate for the detection of adrenal lesions that are 1 cm or greater in diameter.

Technique of MRI

A protocol for imaging the adrenal glands should include chemical-shift imaging in at least two planes. Chemical-shift techniques are sensitive and specific for the identification of intracytoplasmic lipid in tissues that are composed of fat and water. Chemical-shift imaging takes advantage of differences in the water-to-fat ratio of various adrenal lesions and is performed with in-phase and out-of-phase gradient-recalled echo sequences. Respiration-induced motion of the adrenal gland may result in blurred, poor-quality MR images. A breath-hold technique in conjunction with fast imaging is therefore essential to decrease respiratory artifacts. T1- and T2-weighted sequences (see below) and contrast-enhanced imaging with gadolinium are also often utilized for the characterization and staging of known adrenal tumors.

T1- Versus T2-Weighted Images

The signal intensity of a structure on an MR image is dependent upon the proton density, the longitudinal relaxation time (T1), the transverse relaxation time (T2), and flow. Proton density is the concentration of protons in the form of water and macromolecules (fat, protein, etc.). The T1 and T2 relaxation times describe the manner in which the protons revert to their resting states after the initial radiofrequency pulse.

Fat has a higher signal intensity and will appear bright on T1-weighted MR images. Conversely, water yields lower signal intensity and appears dark on T1-weighted images. The normal adrenal gland is homogeneously hypointense compared to the liver and isodense compared to striated muscle on T1-weighted images [7, 16]. If a fat-suppression technique is applied, the gland will appear isointense relative to the liver on T1-weighted images.

T2-weighted imaging relies upon local dephasing of spins following the application of the transverse energy pulse. Fat has a shorter T2 time than water, which means that protons in fat relax or decay more readily than those in water. Since the amount of transverse magnification in fat is small, fat generates less signal intensity on a heavily T2-weighted image. Water has a very high T2 constant and therefore has a very high T2 signal intensity and appears bright on a T2-weighted image. If a fat-suppression technique is applied in T2-weighted MRI, the normal adrenal gland appears slightly hyperintense relative to the liver. T2-weighted images have a 70% overall accuracy for adrenal lesion

characterization, and their value compared to chemical-shift images is limited, particularly for lipid-containing lesions [17]. For nonlipid-containing masses, T2-weighted images may provide additional information.

Gadolinium Enhancement

There is some evidence that gadolinium-enhanced dynamic MRI is better than noncontrast-enhanced MRI for characterizing adrenal tumors [7]. Adenomas demonstrate mild enhancement with a rapid washout, whereas ACCs and other nonadenomatous lesions show strong enhancement with a slower washout, similar to their CT enhancement characteristics. Gadolinium enhancement can also be helpful in staging known adrenal tumors and detecting metastatic disease.

MRI Characteristics of Benign Tumors

With respect to MRI, the most important feature of the adrenal adenoma is the presence of intracellular lipid. Chemical-shift MRI is the most reliable technique for diagnosing this pathology with most adenomas demonstrating a loss of signal intensity on out-of-phase imaging [18]. A decrease in signal intensity on out-of-phase imaging of greater than 20% is diagnostic of an adenoma [19]. The accuracy of MRI in detecting adenomas is 96–100% [20]. Adenomas tend to be slightly hypointense on T1-weighted images and slightly hyperintense on T2-weighted images compared with liver tissue. Immediate contrast-enhanced images show mild, uniform enhancement with quick washout of gadolinium from these benign lesions [21].

MRI cannot differentiate a nonfunctioning adenoma from a functioning adenoma [22]. Like all adenomas, an aldosterone-producing adenoma is isointense to hypointense on T1-weighted images and slightly hyperintense on T2-weighted images compared with the liver. MRI may have a slightly higher sensitivity than CT for distinguishing between a unilateral adenoma and a bilateral hyperplasia, which is essential in determining the subtype of primary hyperaldosteronism [23].

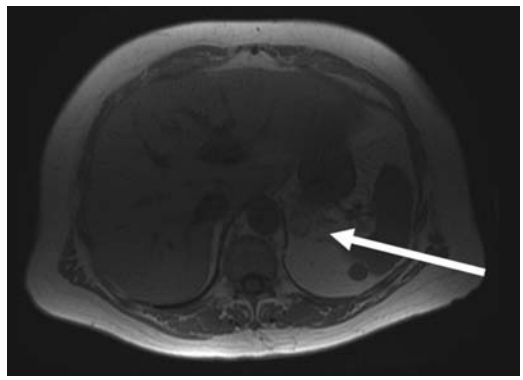

Fig. 25.7. T1 MRI with characteristic hyperintensity of a myelolipoma.

The fatty component of a myelolipoma is hyperintense on nonfat-suppressed T1-weighted images (Fig. 25.7). Fat suppression helps to confirm the diagnosis of myelolipoma by demonstrating a loss of signal intensity within the fatty component.

Simple cysts are hypointense on T1-weighted images and hyperintense on T2-weighted images, with no internal enhancement or soft tissue component.

MRI Characteristics of ACC

On T1-weighted images, ACCs are typically hypointense relative to the liver, whereas on T2-weighted images, ACCs are hyperintense relative to the liver. However, ACCs may appear heterogeneous on both T1- and T2-weighted images owing to internal hemorrhage and necrosis. Blood products in areas of hemorrhage appear bright on T1-weighted images.

An advantage of MRI is its ability to demonstrate flow within blood vessels, which allows visualization of the invasion of ACC into surrounding structures, particularly the inferior vena cava. Of note, right-sided ACCs have a propensity to form venous tumor emboli, and vascular invasion and thrombus can be seen with flow-sensitive MRI sequences [7].

Enhancement after contrast agent administration is usually pronounced around the periphery of ACCs in nonnecrotic areas, and the washout is often prolonged. Functioning ACCs can contain foci of intracytoplasmic lipid,

resulting in a loss of signal intensity on out-of-phase images, while nonfunctioning tumors do not generally have uniform signal loss on out-of-phase images.

MRI Characteristics of Pheochromocytoma

On MRI, pheochromocytomas are typically isointense to hypointense relative to the liver on T1-weighted images and hyperintense on T2-weighted images. The hypervascularity of pheochromocytomas makes them appear characteristically bright, with a high signal intensity on T2-weighted images and no signal loss on opposed-phase images [24, 25]. Although pheochromocytomas may appear very bright, with a "light bulb" appearance, on T2-weighted images, they are typically heterogeneous and of moderately high signal intensity (Fig. 25.8) [26]. T2-weighted images can clearly identify chromaffin tissue; the T2-weighted adrenal mass-to-liver ratio of pheochromocytomas or paragangliomas is usually more than 3. This ratio is much higher than that for adrenocortical adenomas, ACCs, or metastases to the adrenal gland. Thus, MRI may provide some functional (biochemical) information.

Pheochromocytomas enhance after the intravenous administration of gadolinium. There may be some heterogeneity in enhancement due to cystic or necrotic areas. The enhancement may not be pronounced on immediate contrast-enhanced images but may become progressively greater with time on later interstitial-phase images.

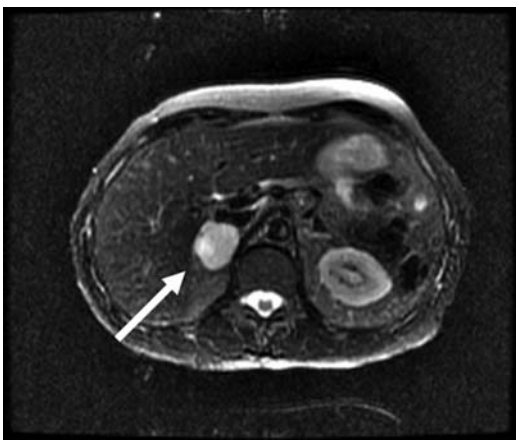

Fig. 25.8. T2-weighted MRI hyperintense pheochromocytoma.

Our practice is to reserve MRI primarily for patients with a biochemically proven pheochromocytoma but negative CT findings. MRI can also be a valuable adjunct in evaluating patients with extra-adrenal sites of pheochromocytoma. MRI is considered slightly superior to CT in the assessment of the relationship between the tumor and the surrounding vessels, particularly with regard to identifying vascular invasion [3]. The detailed anatomic and vascular information can be used to determine resectability and plan the operative approach.

Nuclear Medicine

Nuclear Medicine Overview

Scintigraphic imaging of the adrenal cortex and medulla can provide useful information. Adrenocortical scintigraphy is not frequently performed owing to the widespread use of CT and MRI. However, when CT and MRI are indeterminate, nuclear imaging studies may play a role in assessing the functional status of adrenocortical lesions. Furthermore, scintigraphic imaging of the adrenal medulla and related tissues is useful in providing a definitive diagnosis of pheochromocytoma and paraganglioma.

Positron emission tomography (PET) is an outstanding imaging modality in the evaluation of many different types of malignant processes and has grown in popularity and availability in recent years. This growth has been in part due to the exquisite sensitivity of PET with [^{18}F]fluorodeoxyglucose (FDG) in detecting malignant lesions. FDG exploits the characteristically high glucose consumption of many tumor cells. However, this modality has some limitations. FDG is not a specific tracer for a particular type of cancer and therefore cannot differentiate between types of malignant processes. Moreover, infections and inflammatory conditions can result in prominent FDG uptake, potentially leading to false-positive interpretations of PET studies. Nevertheless, PET and PET/CT with FDG have proven to be extremely useful for the detection of metastases. In addition, FDG-PET has a higher sensitivity and resolution than conventional scintigraphy, making PET an attractive technique to image the adrenal glands.

Adrenocortical Scintigraphy

Radioiodinated NP-59 (^{131}I –6-ß-iodomethyl-19-norcholesterol) is a radioiodinated cholesterol analogue that is bound to and transported by low-density lipoproteins to specific receptors on adrenocortical cells. Once NP-59 is taken up by the cells, it is esterified and stored in the adrenocortical cells without being further metabolized. This allows imaging of the adrenal cortex.

A drawback of scintigraphy with NP-59 is that factors affecting cholesterol uptake into the adrenals also affect uptake of NP-59. Elevated serum cholesterol levels reduce the percentage of radiocholesterol uptake, while an increase in ACTH results in increased NP-59 uptake. In addition, administration of drugs that may interfere with scintigraphic studies must be interrupted: these include glucocorticoids, diuretics, spironolactone, beta and calcium channel blockers, and agents that interfere with the hypothalamic axis and renin–angiotensin–aldosterone system [27]. In addition, NP-59 is not widely available, limiting its widespread use as a routine diagnostic agent.

NP-59's accumulation in the adrenal cortex and background clearance occurs slowly over several days. For routine studies, imaging is usually performed 4–5 days after tracer injection. NP-59 accumulation is greater in the normal adrenal glands than in any other organ but is also noted in the liver, colon, and gallbladder. In normal subjects, activity is usually more intense in the right gland than in the left because of the superimposed liver background activity and decreased soft tissue attenuation on the right side.

Patients should be pretreated with iodine [saturated solution of potassium iodide (SSKI), 1 drop/38 mg three times daily] for at least 1 day before and 7 days after injection of NP-59. This maneuver blocks the uptake of free radioiodine by the thyroid that would otherwise occur. Dexamethasone suppression should be performed in patients with hyperfunctioning of the zona glomerulosa (hyperaldosteronism) or the zona reticularis (hyperandrogenism) of the adrenal. Without suppression of ACTH, the normal high uptake of NP-59 by the zona fasciculata would make interpretation of uptake by the other two zones difficult.

In Cushing's syndrome, the scintigraphic pattern depends on the etiology of hypercortisolism. When a pituitary adenoma causes increased production of ACTH, bilateral early visualization of the adrenal glands is found on scintigraphy. When Cushing's syndrome is due to a glucocorticoid-producing adrenal adenoma, typically only the affected adrenal is visualized on scintigraphy; the affected adrenal adenoma's production of cortisol shuts off pituitary ACTH secretion and shuts off uptake of NP-59 by the contralateral adrenal gland (Fig. 25.9). NP-59

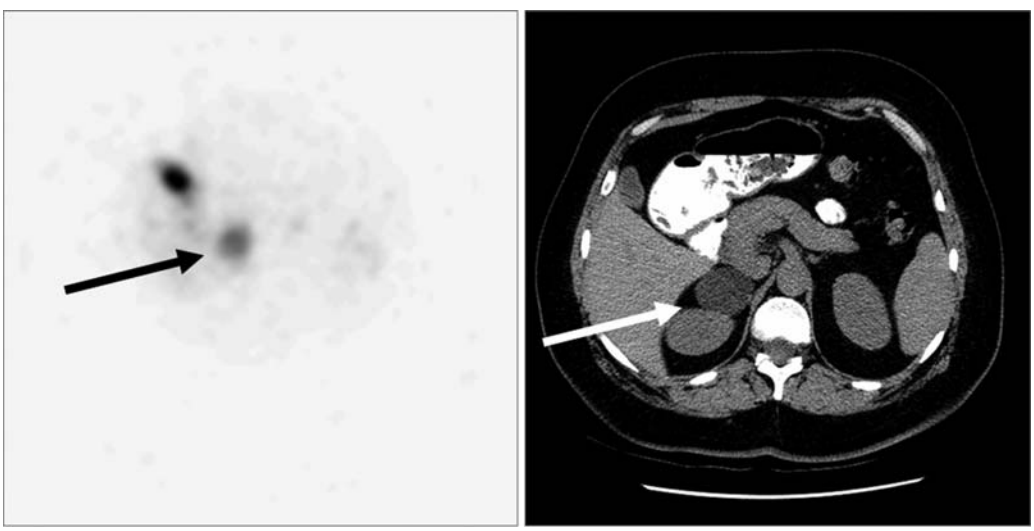

Fig. 25.9. A denotes I-131 and NP-59 Static images and B represents the corresponding CT image in an adenoma of a patient with Cushing's syndrome.

scintigraphy is also useful in patients with Cushing's syndrome to detect postsurgical adrenal remnants that can cause recurrent disease.

In hyperaldosteronism, the distinction between a unilateral adenoma and a bilateral adrenal hyperplasia determines surgical versus medical treatment. Aldosterone-secreting tumors are often small and not easily diagnosed on CT and MRI. While venous sampling has become an attractive diagnostic test, NP-59 is also useful to have in the armamentarium. Dexamethasone suppression is required before scintigraphy. Unilateral early activity on scintigraphy indicates an aldosteronoma, while bilateral delayed activity is more indicative of hyperplasia.

NP-59 scintigraphy provides functional information that may complement the morphologic information provided by CT. Importantly, up to 30% of adrenal tumors cannot be distinguished as benign versus malignant solely using CT characteristics[28, 29]. The presence of concordant (unilateral) CT and NP-59 scans is usually diagnostic of a benign adenoma. The absence of discernible NP-59 uptake by an adrenal tumor strongly suggests either a destructive process or a nonfunctioning lesion such as an ACC or metastasis [30]. A study of 229 patients with abnormal adrenal anatomy on CT found a 100% specificity and a 71% sensitivity of NP-59 scintigraphy in distinguishing benign versus malignant unilateral adrenal masses [30]. The lack of bilateral uptake with functioning ACC may occur because the tumor is unable to incorporate enough tracer per gram of tissue to be visualized, yet secretes sufficient cortisol to suppress ACTH and, thus, the contralateral adrenal gland [31].

The poor tracer uptake by ACC may be due to altered cholesterol metabolism or preferential de novo synthesis of cholesterol by the carcinoma [32]. However, there are several case reports of ACCs (1.8–18 cm diameter) and their metastases that were visualized with NP-59 scintigraphy. In the presence of hormonal excess due to a functioning ACC, unilateral visualization of an adrenal tumor on NP-59 scintigraphy does not always signify benign disease.

Adrenomedullary Scintigraphy

Nuclear medicine imaging is particularly useful in patients with biochemical evidence of a functioning adrenergic adrenal tumor that has not been localized by CT or MRI and in the follow-up evaluation of patients with suspected or documented recurrent or metastatic disease. Scintigraphic studies of the adrenal medulla make use of the norepinephrine analogue meta-iodobenzylguanidine (MIBG), a tracer that is taken up and localized in the storage vesicles of presynaptic adrenergic nerves. In addition to being taken up by the adrenal medulla, MIBG localizes to the heart and spleen, two other organs with rich adrenergic innervation and to the liver, an organ that processes catecholamines for excretion.

Certain drugs interfere with MIBG uptake and must be stopped prior to scanning, some of them for up to 21 days. These include sympathomimetics, reserpine, guanethidine, bretylium, calcium channel blockers, labetalol, ACE inhibitors, tricyclic antidepressants, and cocaine [8].

Radiotracers paired with MIBG include ^{123}I and ^{131}I, the former affording a lower radiation dose and the latter allowing delayed imaging. ^{123}I-MIBG is at present the principal tracer for diagnostic purposes. The use of ^{131}I-MIBG for diagnostic applications is largely outdated; however, this radiopharmaceutical is used to treat metastatic malignant pheochromocytoma, paraganglioma, and neuroblastoma. A prerequisite to therapeutic ^{131}I-MIBG is demonstrated tracer uptake on a diagnostic study using ^{123}I-MIBG.

To prevent thyroid ablation, radiotracer uptake by the thyroid must be blocked by administering SSKI or potassium perchlorate before and after administration of ^{123}I-MIBG or ^{131}I-MIBG. The usual intravenously administered dose of ^{123}I-MIBG is 10 MCi/cm^2 body surface and ^{131}I-MIBG is 0.5 mCi/1.7 cm^2. Initial imaging is usually performed between 4 and 6 h after administration of ^{123}I-MIBG; delayed imaging is performed at 24 h. However, when ^{131}I-MIBG is used, optimal imaging is at 48–72 h, and multiple scans may be needed over 72 h to get the best possible image.

In ^{131}I-MIBG scintigraphy, faint visualization of the normal bilateral adrenal medulla is seen in only 10% of patients. In ^{123}I-MIBG imaging, the normal adrenal medulla is visualized more frequently. When pheochromocytoma is present, the characteristic appearance is a unilateral focus of uptake (Fig. 25.10).

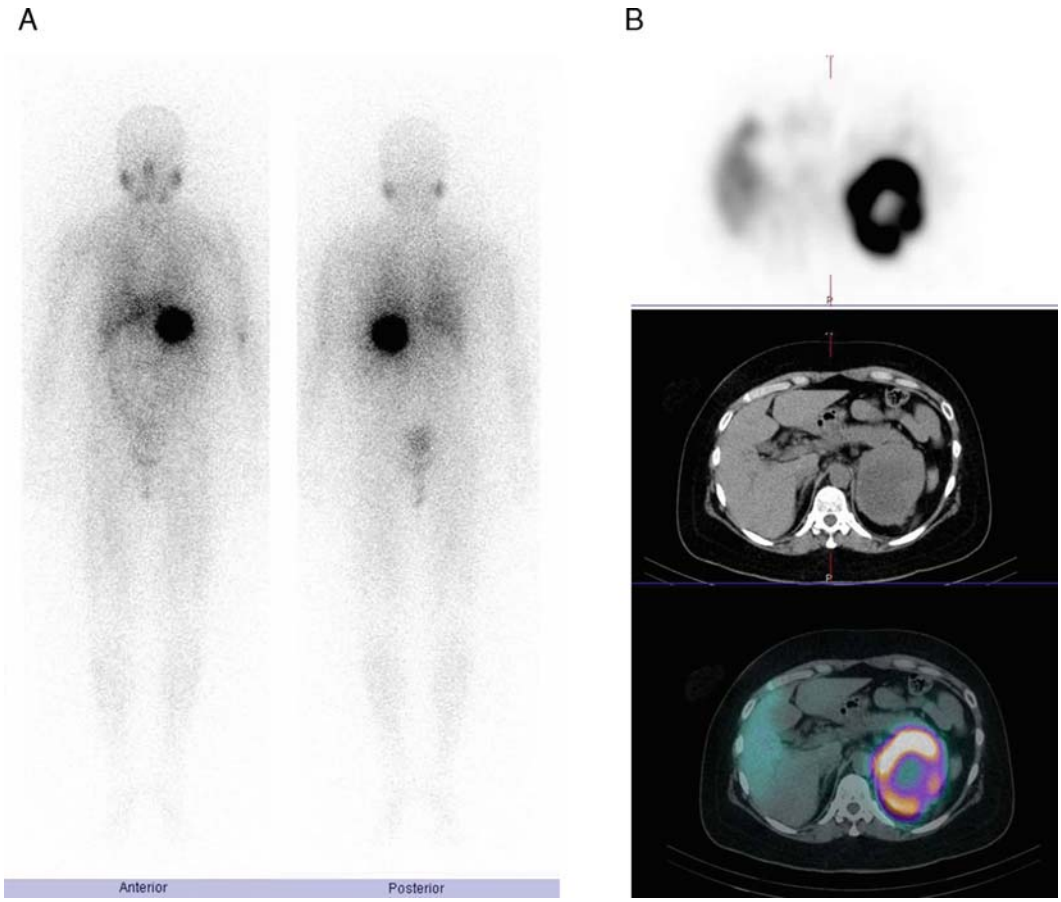

Fig. 25.10. (**A**) Anterior and posterior whole-body views of an ^{123}I-MIBG scan done at 24 h after injection, in a middle age woman with pheochromocytoma. The MIBG avid tumor is visualized in the left adrenal gland. (**B**) Corresponding SPECT/CT of the abdomen, clearly delineating the rim of increased ^{123}I-MIBG activity to the large left adrenal mass. The center of the mass is not MIBG avid due to tumor necrosis. No distant metastases are visualized.

We reserve ^{123}I-MIBG scanning for use in patients with biochemical evidence of pheochromocytoma in whom CT or MRI has failed to identify the tumor or who have lesions greater than 5 cm on CT or MRI because of the concern for metastasis. It may also be helpful in patients with distorted anatomy due to previous surgery or with equivocal biochemical diagnoses.

^{131}I-MIBG scanning offers specificity ranging from 95 to 100% but has lower sensitivity [45]. Despite recent optimization in acquisition and processing protocols, ^{123}I-MIBG scintigraphy interpretation remains challenging. False-positive studies are normally due to artifactual findings. False-negative scans have several possible causes, such as size of the lesion, physiologic tracer uptake masking a focus of disease, or decreased uptake as a result of pharmaceutical interference by other drugs. Therefore, MIBG scintigraphy is often reviewed in conjunction with, and compared to, other imaging modalities such as CT and MRI.

Over the past few decades, there have been attempts to coregister nuclear medicine images with images from conventional modalities such as CT and MRI [33, 34]. However, the rather cumbersome and time-consuming coregistration algorithms have limited the use to research applications. Nevertheless, over the past few years, single photon emission computed tomography

(SPECT)/CT scanners have entered the market, providing the fusion of functional (MIBG) images and anatomic (CT) images. Moreover, newer SPECT/multislice CT scanners that have recently become commercially available may overcome some of the limitations of conventional whole-body planar CT and SPECT imaging.

SPECT/CT has been shown to improve the delineation of physiologic diffuse intraluminal bowel activity, the localization of tumor sites, and the detection of bone and bone marrow involvement. SPECT/CT can also optimize the characterization of tumor recurrence adjacent to organs with physiologic high MIBG uptake, such as the heart, kidneys, and liver [35]. The superb coregistration of the fusion images that can be obtained with today's state-of-the-art SPECT/multislice CT scanners can help avoid false-positive and false-negative interpretations.

Positron Emission Tomography

There is an increasing body of knowledge on the use of PET and PET/CT for the noninvasive assessment and characterization of lesions of the adrenal glands [31]. FDG is the only commercially available PET tracer approved by the US Food and Drug Administration that can be used for the evaluation of the adrenal glands. However, several other PET tracers under investigation have provided very encouraging results in the evaluation of lesions of the adrenal cortex and medulla and in the assessment of patients with an incidentally discovered adrenal mass [36].

PET or PET/CT with FDG is excellent at differentiating between benign and malignant adrenal lesions, both primary ACCs and lesions metastatic to the adrenal gland. FDG is a nonspecific tumor-imaging agent whose uptake in tumor cells (measured as standard uptake values, SUVs) is based on increased glucose metabolism in malignant lesions (Fig. 25.11). Over the past few years, the reported accuracy of PET/CT for differentiating metastatic adrenal lesions from benign adrenal lesions in oncologic patients has ranged between 92 and 100% [37, 38]. In distinguishing benign from primary malignant adrenal lesions, many studies describe 100% sensitivity and specificity [39, 40]. In one of the largest studies, Metser et al. used FDG-PET/CT to characterize adrenal masses in 150 patients. With a cutoff SUV of 3.1 or higher to define malignant lesions, FDG-PET alone had a sensitivity of 98.5% and a specificity of 92% for characterizing lesions as benign or malignant; the addition of CT to PET increased the specificity to 98% [41].

FDG-PET and FDG-PET/CT have also been used for the evaluation of patients with pheochromocytomas since this type of tumor usually exhibits increased FDG uptake. Shulkin et al. identified pheochromocytomas with FDG-PET in 22 of 29 patients. In that study, pheochromocytomas that poorly concentrated MIBG were depicted with FDG, and conversely, all tumors that could not be imaged with FDG were detected with MIBG [42].

Other PET tracers are being developed to evaluate the adrenal gland. However, for now, these tracers are limited to the research arena. Moreover, since several of these tracers are labeled with the short-lived ^{11}C isotope, their use is limited to a few institutions with on-site cyclotrons and sophisticated radiosynthesis facilities.

For functional imaging of the adrenal cortex, ^{11}C-metomidate (MTO) is currently being investigated as a novel tracer. MTO binds specifically to 11β-hydroxylase, an enzyme that is essential in the biosynthesis of cortisol and aldosterone and is regulated by ACTH [31]. Minn et al., in a study of 16 patients with adrenal masses, found that ^{11}C-MTO PET clearly separated 13 adrenocortical lesions (including both nonfunctioning and functioning lesions: adrenocortical adenomas, ACC, and macronodular hyperplasia) from three noncortical lesions (benign and malignant pheochromocytoma and metastasis to the adrenal) [43]. However, ^{11}C-MTO PET could not distinguish benign adrenocortical tumors from ACC. In contrast, FDG-PET separated all malignant lesions from benign adrenal masses, showing a specificity, sensitivity, and diagnostic accuracy of 100% for the characterization of adrenal masses.

The number of PET tracers that target catecholamine synthesis or reuptake pathways continues to increase and now includes ^{11}C-epinephrine, ^{11}C-hydroxyephedrine,^{18}F-fluorodopamine (^{18}F-FDA), and ^{18}F-fluorodihydroxyphenylalanine (^{18}F-DOPA). These agents take advantage of the

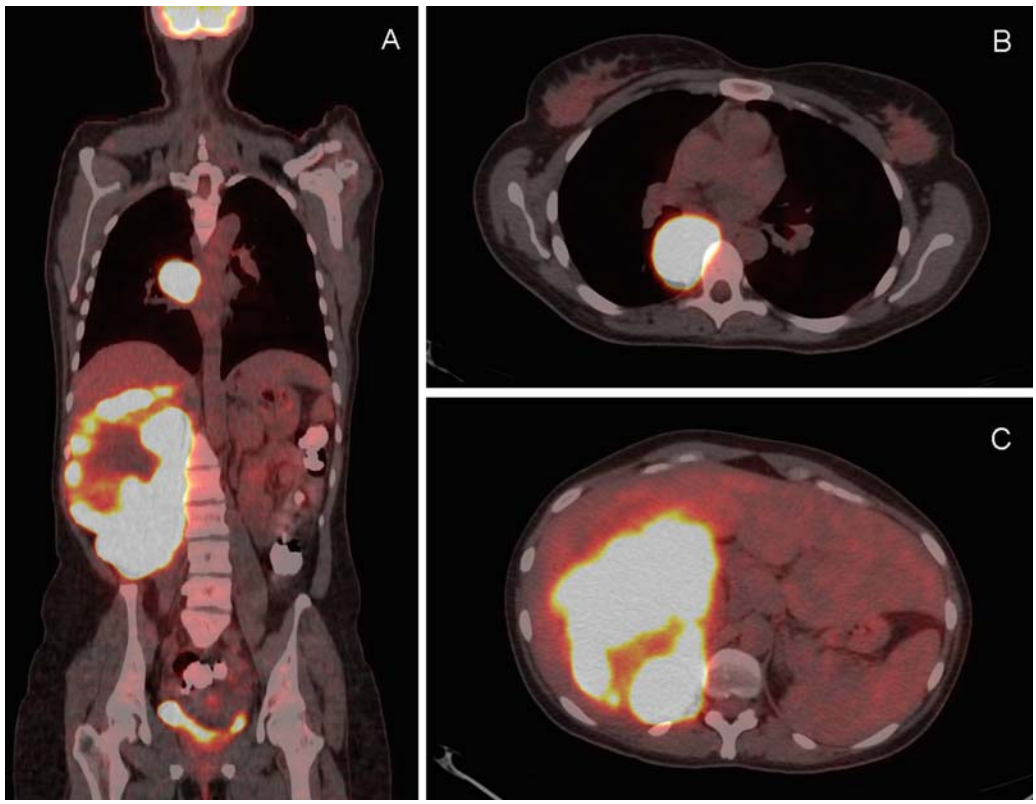

Fig. 25.11. FDG PET/CT images of a young woman with metastatic recurrent right adrenal cortical carcinoma. Study requested for restaging of disease. (**A**) Coronal view of the PET/CT scan, which shows the large and metabolically very active recurrent tumor in the right adrenal bed of 16.5 × 12.3 cm (SUV = 43.6), and the metastatic lesion to the posterior mediastinum (SUV = 40.3). (**B** and **C**) Axial images of the PET/CT scan at the level of the chest and upper abdomen, respectively, demonstrating the tumor lesions.

unique characteristics of catecholamine biosynthesis and metabolism in the adrenal medulla and have high sensitivity and specificity for the localization of pheochromocytomas, neuroblastomas, and related neoplasms. Somatostatin receptors are widely distributed in neoplasms of the neural crest, and based upon the earlier success of single-photon-labeled somatostatin receptor-imaging agents, numerous somatostatin antagonists labeled with positron-emitting isotopes have been developed [44].

^{18}F-FDA, ^{18}F-DOPA, ^{11}C-epinephrine, and ^{11}C-hydroxyephedrine have all been demonstrated to image pheochromocytomas and related neoplasms. In a study using ^{11}C-hydroxyephedrine PET, rapid and early imaging – approximately 10 min postinjection – was reported in 9 of 10 patients with pheochromocytomas [45]. Mann et al. evaluated 14 patients, 8 of whom had proven pheochromocytoma, using ^{11}C-hydroxyephedrine PET, FDG-PET/CT, and ^{131}I-MIBG. ^{11}C-hydroxyephedrine detected all sites of disease. FDG-PET/CT was successful in depicting all sites of adrenal and soft tissue metastatic disease, except metastases to bone, whereas ^{131}I-MIBG localized to confirmed sites of disease in only four of eight patients [46]. In a study of ^{18}F-FDA-PET in 16 patients with metastatic pheochromocytoma, ^{18}F-FDA correctly identified all sites of metastatic pheochromocytoma, including some metastatic lesions that were not detected with ^{131}I-MIBG scans [47].

For diagnosis of pheochromocytoma the functional imaging test of choice today is ^{123}I-MIBG, if possible including SPECT/CT. If the MIBG scan is negative, then PET using a specific noradrenergic transporter system-

targeting agent such as ^{18}F-FDA or ^{18}F-DOPA should be employed. If these studies are negative, the tumor has likely undergone dedifferentiation and is probably malignant. Therefore, in these instances, imaging with FDG-PET, FDG-PET/CT, or ^{111}In-pentetreotide (Octreoscan) PET is recommended [48].

Role of Nuclear Medicine in Incidentalomas

The routine use of high-resolution imaging techniques for the evaluation of many oncologic and nononcologic disease processes has led to the identification of an increasing number of unsuspected adrenal lesions, or incidentalomas. In this situation, the diagnostic algorithm begins with biochemical evaluation to assess for hormone hypersecretion, since hormonally active adrenal masses require surgical resection. Despite the excellent anatomic and structural detail that CT and MRI provide, functional adrenal imaging using targeted radionuclides, such as NP-59, MIBG, and FDG, offers the best diagnostic sensitivity and specificity for characterizing incidentalomas. These tracers target entirely separate physiologic processes, and they can be used selectively, based on clinical setting and biochemical data, to identify different types of adrenal tumors. The role of radionuclide imaging in the evaluation of nonfunctioning incidentalomas has also been unequivocally demonstrated.

In a study by Maure et al. of 54 patients with incidentalomas, NP-59 imaging had a positive predictive value of 89% for characterizing an adrenal mass as an adenoma; the negative predictive value to rule out this type of tumor was 100%. The positive predictive value of ^{131}I-MIBG imaging for characterizing an adrenal mass as a chromaffin tumor was 83%, and the negative predictive value to rule out this type of tumor was 100% [39].

In addition to the importance of well-established high-resolution imaging techniques, there is increasing scientific documentation of the benefits of functional adrenal imaging. The availability of hybrid imaging techniques, including PET/CT and SPECT/CT, allows the simultaneous evaluation of adrenal function and anatomy. In addition, the recent introduction of selective PET tracers that target specific biosynthetic pathways has created an impetus for the development of novel approaches in adrenal imaging.

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26

Adrenal Venous Sampling

Radu Mihai and Gregory P. Sadler

Introduction

Interventional radiology has become a major tool in the localization of endocrine tumours. Inferior petrosal sinus sampling for patients with Cushing's disease, selective parathyroid venous sampling for patients with persistent hyperparathyroidism, hepatic venous sampling with arterial stimulation for patients with pancreatic neuroendocrine tumours and adrenal venous sampling (AVS) for Conn's tumors are currently used in all tertiary endocrine centers [1].

In the adrenal disease, cross-sectional anatomical imaging using computer tomography (CT) and magnetic resonance imaging (MRI) can lateralize the side of adrenal tumors in patients with Cushing's syndrome, pheochromocytoma or adrenal cancer. The vast majority of these patients have tumors located in one adrenal gland with sufficient size to be identified by the above scans. The contralateral gland is usually atrophic or of normal size. In contrast, patients with primary hyperaldosteronism (PHA) have small tumors, frequently less than 20 mm, that can be difficult both to demonstrate and to differentiate from other nonfunctioning benign adrenal adenomas.

Anatomy of Adrenal Venous Drainage

Adrenal glands receive arterial supply from numerous small branches from the phrenic artery, renal artery, and aorta. These branches create a plexus of capillaries under the adrenal capsule from which blood drains through the adrenal cortex into small venous branches collecting finally into a single central adrenal vein. On the right side, a short adrenal vein drains directly into the vena cava. Additional small branches can sometime be present. On the left side, the adrenal vein drains into the renal vein.

Indications for AVS

The most common indication for AVS is the need to demonstrate unilateral excessive aldosterone secretion in patients with PHA, thus localizing the tumor. Rarely AVS may be used in patients with biochemical diagnosis of phaeochromocytoma in whom conventional radiology demonstrates bilateral micro or macro modularity. In a minority of such patients only one adrenal gland is the source of excessive catecholamine secretion and they can be potentially spared having to undergo a bilateral adrenalectomy if unilateral hypersecretion can be demonstrated.

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Primary Hyperaldosteronism

PHA is due to autonomous aldosterone secretion from the adrenocortical zona glomerulosa. This leads to suppressed renin, hypertension, and in more severe forms, hypokalemia. The most common types of PHA are

- aldosterone-producing adenomas (Conn's syndrome), accounting for approximately a third of cases;
- idiopathic bilateral adrenal hyperplasia, accounting for about two thirds of cases;
- primary adrenal hyperplasia, a rare condition defined as angiotensin-II resistant tumors or multinodular adenomas on a background of adrenal hyperplasia;
- familial forms of PHA (very rare):
    - *Glucocorticoid-remediable aldosteronism* (familial hyperaldosteronism type I) is an autosomal dominant disorder caused by a hybrid gene mutation formed by a cross over between the ACTH-responsive regulatory portion of the 11β-hydroxylase (CYP11B1) gene and the coding region of the aldosterone synthase (CYP11B2) gene. High levels of the abnormal adrenal steroids 18-oxocortisol and 18-hydroxycortisol are produced under the control of ACTH and are suppressible by physiological doses of exogenous glucocorticoids.
    - *Familial hyperaldosteronism type II* is a very rare condition with autosomal dominant inheritance whose precise genetic cause remains to be elucidated. Such patients have autonomous aldosterone hypersecretion which is not suppressible by dexamethasone [2].

There is a clear need to differentiate between patients with aldosterone-producing adenomas (i.e., Conn's syndrome) and patients with bilateral adrenal hyperplasia. The first group can be cured by unilateral adrenalectomy. In the second group, surgery is not indicated and patients should receive targeted medical treatment with mineralocorticoid receptor antagonists [3, 4].

Incidence of Hyperaldosteronism in Unselected Hypertensive Patients

A lack of a universally accepted definition means the exact prevalence of PHA cannot be determined. Additionally, there is a failure to identify patients during the normotensive and/or normokalemic phases in the evolutionary development of a disease eventually characterized by hypertension and hypokalemia.

Formerly, fewer than 1% of patients with hypertension were believed to have PHA, and hypokalemia was considered a prerequisite for pursuing diagnostic tests for PHA. The "rediscovery" in the last decade of the normokalemic phase of PHA (originally described by Jerome Conn) and the wide application of screening with aldosterone/renin ratio in all hypertensive patients have triggered a potential "epidemic" of PHA in recent years.

Currently, PHA is regarded as the commonest potentially curable form of hypertension identified in at least 5–10% of unselected hypertensive patients (up to 30% in some series). Such findings could translate into many millions of patients.

To illustrate this, in a retrospective review of practice in centers in five continents, the application of screening with aldosterone/renin ration led to a 5- to 15-fold increase in the identification of PHA and up to sixfold increase in the annual detection rate of aldosterone-producing adenomas [5]. Similarly, one Australian Unit reported that the decision to screen all (not just hypokalemic or resistant) hypertensives by aldosterone/renin ratio testing led to a 10-fold increase in detection rate of PHA and fourfold increase in removal rate of aldosterone-producing adenomas [6].

A very high incidence of PHA (19%) was detected in 420 hypertensive patients from Central Europe (Czech Republic) [7]. In an analysis of 305 Italian hypertensive patients, 10% were found to have PHA, a much higher incidence than in a control group of normotensives (1.5%) [8]. A proven (minimum) incidence for PHA of 8.5% was demonstrated in a study of 199 normokalemic hypertensives demonstrating that restricting investigations only to hypokalemic hypertensives will lead to an underestimation of the true incidence of PHA [9].

Similarly, in a study of 1,180 consecutive hypertensive patients presenting in 14 centers, an average of 4.8% had aldosterone-producing adenomas, with a higher incidence in centers were adrenal sampling was available [10]. Similar figures have been reproduced in studies on hypertensive Chinese patients [11].

Interestingly, a PHA incidence of 5.5% was also found in a group of 125 normokalemic patients with solid adrenal incidentalomas [12].

Despite this growing enthusiasm, some clinicians have raised concerns regarding widespread use of aldosterone/rennin ratio as a routine part of assessment of all hypertensives. Such authors highlight the risk that such protocols will lead to massive increases in costs, both in money and in morbidity, while providing benefit to only a very small number of patients [13].

Diagnostic Tests Performed Before Proceeding to AVS

Aldosterone/renin ratio is the screening test of choice for PHA. The cutoff levels vary between laboratories (range 20:1 to 50:1 if PAC is expressed as ng/dl and PRA in ng/ml/h). Posture and time of sampling should be standardized both within and between centers to minimize variability in cutoff levels [14]. An alternative screening test is the measurement of aldosterone/renin ratio after 50 mg Captopril [15].

Antihypertensive therapy can interfere with the interpretation of aldosterone/renin ratio. False-positive results can be obtained in patients on beta-blockers, clonidine, nonsteroidal antiinflammatories, and the contraceptive pill. False-negative results can be obtained in patients on diuretics, ACE inhibitors, calcium channel blockers, patients with reno-vascular hypertension or malignant hypertension, and patients on very-low sodium diets. However, a positive screening result is *not diagnostic* and requires a confirmatory test.

Aldosterone suppression test after oral salt loading. The diagnosis of PHA is further suggested by an inability to suppress aldosterone production (estimated from urine aldosterone concentration) with a high sodium diet. Similarly, PHA is confirmed by the failure to suppress plasma aldosterone concentration to below 10 ng/dl after intravenous salt loading with 2 l of N-saline during 2–4 h, even though the test is positive in only 3/10 patients with Conn's syndrome.

Once the diagnosis of PHA has been established, it is necessary to exclude glucocorticoid-remediable aldosteronism. Subsequently there is a need to differentiate unilateral versus bilateral disease and then proceed to localization studies.

Posture test. The bedside posture test was originally promoted as a means of identifying patients with aldosterone-producing adenomas. In patients with idiopathic PHA (i.e., bilateral adrenal hyperplasia) plasma aldosterone concentration usually increases after standing for 4 h, whereas a postural decrease in aldosterone levels is seen in patients with unilateral disease (i.e., Conn's syndrome). This phenomenon is due to the fact that aldosterone-producing adenomas are unresponsive to angiotensin but still follow the circadian rhythm of ACTH/cortisol axis. The test can produce false-negative results and the overall accuracy was calculated to be 85% in a series of 246 patients pooled from 16 studies [16]. A report from the National Institutes of Health on 48 patients with PHA found that the posture test could identify as many as 30% with a unilateral source and the authors concluded that the posture test was an important step in the decision-making tree leading to surgical intervention.

Adrenal Imaging. CT scan is the initial localization procedure. If a solitary unilateral macroadenoma larger than 1 cm is found in the presence of a normal contralateral adrenal gland, some authors would argue that no other localization studies are necessary and unilateral adrenalectomy can be considered.

This view is supported by a series of 50 patients where adrenalectomy was performed in 35 patients (70%) solely on the information offered by CT scans, and all these patients were cured [17]. Similarly, in a series of 60 patients from San Francisco 80% of patients had their adrenal tumours lateralized based on CT scans, MRI, or both. All patients achieved biochemical cure [18].

In contrast, in a series of 203 PHA patients the Mayo Clinic reported that based on CT findings alone, 42 patients (22%) would have been incorrectly excluded as candidates for adrenalectomy, and 48 (25%) might have had unnecessary or inappropriate adrenalectomy [19]. In a further study of 62 patients, CT imaging was either inaccurate or provided no additional information in 68% of the patients with primary aldosteronism, suggesting that adrenal CT imaging alone is not a reliable method to differentiate between different causes of primary aldosteronism [20].

Adrenal Venous Sampling

Formerly, AVS was usually reserved for patients in whom both CT and isotope scanning of the

adrenals were inconclusive and not able to reliably distinguish between unilateral and bilateral adrenal aldosterone hypersecretion. For this subgroup of patients adrenal vein sampling is essential to establish the correct diagnosis of PHA [21]. For example, in one study the results of AVS altered the management in 14 of 18 patients, suggesting AVS is essential in patients with equivocal CT scans to avoid unnecessary and inappropriate adrenalectomy [22]. Functional adrenal isotope scanning has largely been abandoned and indeed is no longer available in the UK. More recently AVS has become an integral part of the preoperative work up of patients with Conn's tumor in many large centers.

Protocol for AVS

Patients are maintained recumbent overnight, prior, and during the procedure. Relaxation techniques may be used to eliminate stress response.

CT is useful in planning adrenal vein sampling by demonstrating the anatomy and positions of the adrenal veins. A small amount of contrast material is injected gently and slowly into the adrenal vein; it is not necessary to perform formal venography to outline the entire gland.

Simultaneous blood samples from each adrenal vein, renal veins, inferior vena cava, and peripheral (antecubital) vein are drawn for plasma aldosterone and cortisol measurement. All aldosterone measurements are normalized according to the cortisol concentration in the sample.

The use of adrenocorticotropic hormone (ACTH) stimulation during AVS remains debatable. Infusion of ACTH before and during the procedure minimizes episodic changes in aldosterone secretion caused by stress-induced endogenous ACTH release.

Some physicians argue that defining contralateral suppression in patients with Conn's syndrome is facilitated by ACTH stimulation. In contrast, others found that lateralization of aldosterone secretion side did not improve: in a prospective study of 24 consecutive patients a high-dose ACTH (250 μg intravenous) bolus administered at the beginning and 30 min into the procedure led to a significant increase of aldosterone from contralateral adrenal vein blood, but not from the APA gland. Such results do not support the usefulness of high-dose ACTH testing to improve the diagnostic accuracy of AVS [23].

This topic was explored further in a study of 31 patients. In half the procedures, simultaneous bilateral adrenal venous catheterization and sampling was performed before and after intraprocedural ACTH administration. In the remaining half, sequential catheterization of the left and right adrenal veins was performed during continuous ACTH infusion 1 h before and throughout AVS. Simultaneous bilateral AVS localized unilateral disease in seven of eight cases (88%) and was nondiagnostic in one case (13%). Sequential bilateral AVS localized unilateral disease in four of four cases (100%). Baseline (prestimulation) sampling did not contribute unique diagnostic information in any case and provided contradictory or confounding information in 3 of 11 simultaneous AVS procedures (27%). Both simultaneous and sequential AVS are adequate studies; however, obtaining baseline prestimulation samples during simultaneous AVS is unnecessary and increases the cost of the procedure [24].

Criteria for Positive Localization

To confirm that the vein is draining the majority of adrenal cortical blood, the adrenal vein sample should have a significantly higher level of cortisol than a peripheral sample. Access to the adrenal veins is considered successful if the cortisol gradient (central to peripheral) exceeds 2.0. Success rate of cannulation varies between centers and is likely to be increase with experience. Some achieved a 95% success rate [25], while others reported success in only 75% [26].

Adrenal glands that are producing excess aldosterone demonstrate an aldosterone/cortisol ratio that is higher than the peripheral value. A central/peripheral aldosterone ratio more than 3.0 was accepted as evidence of an ipsilateral (autonomous) lesion, whereas ratios less than 2.0 were taken as evidence of contralateral suppression (i.e., sampling from the uninvolved gland) provided the cortisol central/peripheral ratio exceeded 10.

The criteria used to establish unilateral autonomy (dominance) differ. Doppman et al.

[27] emphasized the importance of identifying contralateral adrenal suppression in localizing the abnormal gland. Other reports have placed more emphasis on the differential aldosterone output from the two glands.

When bilateral access is not achieved, lateralization can still be demonstrated when only one adrenal vein (the contralateral) is accessed.

Of 39 patients who underwent adrenalectomy for presumed unilateral disease, only 16 patients had "ideal" AVS, and 18 patients had only unilateral cannulization on AVS. Despite this, 11 appeared to lateralize and 7 had imaging to support unilateral disease. Postoperatively, 15 (82%) had a significant reduction in their blood pressure, and 7 (39%) of these were cured. Surgery failed in two patients; both were found to have bilateral hyperplasia. Bilaterally unsuccessful cannulization (n = 5) still lateralized in three patients, and two patients had nodules on computed tomography scan. All five patients had significant reduction in blood pressure, and two were cured. Following "less than ideal" AVS, clinical decisions can still be made using anatomic and partial AVS data [28].

Complications

The technique is technically demanding, invasive, and is associated with a recognized morbidity including bleeding (1–5%), rupture/thrombosis of adrenal veins, and adrenal infarction (1%). Despite the limitation and potential morbidity, AVS should be performed in specialized endocrine centers for selected patients with PAH when diagnostic difficulty arises with conventional imaging. This diagnostic tool can facilitate the management strategy, especially with reference to the adoption of surgical treatment, in patients with PHA.

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27

Primary Hyperaldosteronism

Joseph DiNorcia and James A. Lee

Introduction

In 1955, Dr. Jerome Conn described a female patient with signs of hypertension and hypokalemia and symptoms of weakness and polyuria [1]. Exploratory laparotomy led to the resection of an adrenocortical adenoma. The patient's blood pressure and metabolic derangements normalized after the operation, leading Conn to hypothesize that these signs and symptoms were due to the adenoma's excessive secretion of aldosterone.

True Conn's syndrome is hyperaldosteronism secondary to an aldosterone-producing adenoma, though other causes of aldosterone excess have been identified. This chapter explores the causes of primary hyperaldosteronism. After a brief review of the relevant physiology, we will delineate the various subtypes of primary hyperaldosteronism and then examine the epidemiology, pathologic features, clinical characteristics, diagnostic methods, localizing studies, and ultimate treatment options for this potentially curable cause of hypertension.

Physiology

Aldosterone, the potent mineralocorticoid secreted by the zona glomerulosa of the adrenal cortex, regulates the body's fluid and electrolyte balance by stimulating sodium retention and potassium and hydrogen ion secretion in the distal convoluted tubules of the kidneys [2, 3]. Aldosterone also promotes sodium absorption by other epithelia, including the salivary and sweat glands and the gastrointestinal mucosa. The ultimate effect is increased salt load which increases water retention. Hyperaldosteronism thus leads to expansion of the intravascular volume at the expense of potassium and hydrogen ions, resulting in hypertension, hypokalemia, and alkalosis [4].

The renin–angiotensin system is a principal regulator of aldosterone secretion (Fig. 27.1). In response to decreased renal perfusion, decreased plasma sodium concentration, or sympathetic nervous system stimulation, the juxtaglomerular cells of the kidney release renin. Renin enzymatically cleaves angiotensinogen (produced in the liver) to angiotensin I. Angiotensin-converting enzyme (ACE) in the lungs and endothelium then cleaves angiotensin I to form angiotensin II. Angiotensin II directly stimulates aldosterone biosynthesis and release from the adrenal gland, increasing sodium absorption and expanding the intravascular volume in an effort to increase renal blood flow. Potassium and to a lesser degree adrenocorticotropic hormone (ACTH) also regulate aldosterone secretion, but their implications are less relevant to this discussion [4, 5].

General Considerations

Hyperaldosteronism can be divided into primary and secondary forms (Table 27.1). Primary hyperaldosteronism is characterized by autonomous

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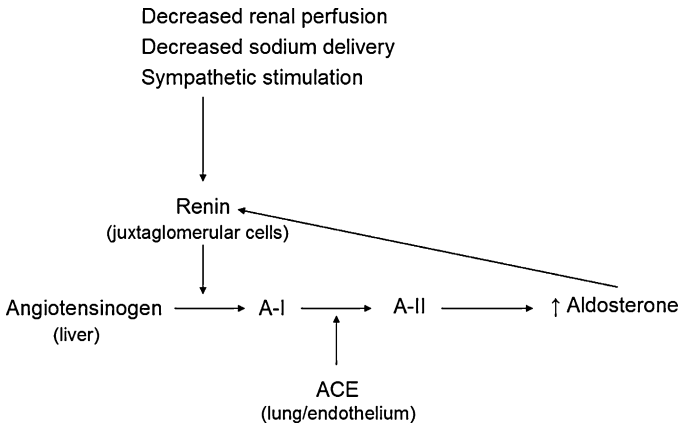

Fig. 27.1. A schematic diagram illustrates how the renin–angiotensin system regulates aldosterone production.

Table 27.1. Causes of Hyperaldosteronism

Primary Hyperaldosteronism
Aldosterone-producing adrenocortical adenoma (2/3)
Idiopathic bilateral adrenal hyperplasia (1/3)
Aldosterone-producing adrenocortical carcinoma (<1%)
Unilateral adrenal hyperplasia (<1%)
Familial hyperaldosteronism, Types I and II (<1%)
Secondary Hyperaldosteronism
Renal artery stenosis
Congestive heart failure
Cirrhosis
Pregnancy

adrenal hypersecretion of aldosterone with consequent suppressed plasma renin levels. Primary hyperaldosteronism has several subtypes. Aldosterone-producing adrenocortical adenoma (aldosteronoma) and idiopathic hyperaldosteronism (bilateral adrenal hyperplasia) are the most common causes and account for 95% of all cases [6–10]. Uncommon causes include aldosterone-producing adrenocortical carcinoma, unilateral adrenal hyperplasia, familial hyperaldosteronism type 1 (glucocorticoid-suppressible hyperaldosteronism), and familial hyperaldosteronism type 2 [11, 12]. Familial hyperaldosteronism type 1 is an autosomal dominant genetic disorder that results from the fusion of the ACTH-responsive 11-beta-hydroxylase gene promoter to the coding sequence of the aldosterone synthase gene. Aldosterone synthesis thus is under ACTH stimulation resulting in excess aldosterone production [13, 14]. Patients have a family history of early onset hypertension. Diagnosis can be made by measuring 24 h urine samples for elevated 18-hydroxycortisol and 18-oxocortisol levels or by genetic testing [15, 16]. Exogenous glucocorticoid therapy with agents such as dexamethasone suppresses ACTH and the overproduction of aldosterone, normalizing both blood pressure and potassium levels [12, 17]. Familial hyperaldosteronism type 2 is another rare cause and refers to the familial occurrence of aldosterone-producing adrenocortical adenoma, unilateral adrenal hyperplasia, or both [18–21].

The appropriate surgical or medical treatment of primary hyperaldosteronism depends on the correct differentiation of the various subtypes. Aldosterone-producing adrenocortical adenoma, for example, is treated by unilateral adrenalectomy. Idiopathic hyperaldosteronism, on the other hand, does not respond to adrenalectomy and is treated with aldosterone antagonists. From a treatment standpoint, the subtypes of primary hyperaldosteronism thus can be divided into two groups: (1) unilateral adrenal aldosterone hypersecretion that is amenable to surgical resection (e.g., aldosteronoma, unilateral hyperplasia, carcinoma, and familial hyperaldosteronism type 2) and (2) bilateral adrenal aldosterone hypersecretion that is managed medically (e.g., idiopathic hyperaldosteronism and familial hyperaldosteronism type 1) [6, 7].

In secondary hyperaldosteronism, the adrenal glands function normally, and increased plasma renin levels stimulate the hypersecretion of aldosterone. Conditions associated with elevated plasma renin levels such as renal artery stenosis, congestive heart failure, cirrhosis, and normal pregnancy cause increased plasma aldosterone levels [22, 23]. Renin-secreting tumors are another rare cause of secondary hyperaldosteronism [24]. Treatment of secondary hyperaldosteronism involves management of the underlying condition.

Epidemiology

Primary hyperaldosteronism is twice as common in women as in men, usually occurring between ages 30 and 50 [25, 26]. Early studies indicated that primary hyperaldosteronism was an uncommon cause of hypertension with a prevalence of <1 to 2% [8, 27]. In these studies, hypokalemia was thought to be a necessary finding, and screening thus was limited to patients with low potassium levels [28–30]. More recent studies have shown that the majority of patients with primary hyperaldosteronism have normal potassium levels, indicating that the early studies likely underestimated the true prevalence [31–33]. In addition, with the more widespread use of the plasma aldosterone concentration (PAC) to plasma renin activity (PRA) ratio as a screening test in patients with resistant hypertension or who are on multiple medications, the detection of primary hyperaldosteronism is increasing [33–41]. The true prevalence is between 5 and 13% in general hypertensive populations [8] and perhaps as high as 20% in patients with resistant hypertension [42, 43].

Controversy persists, however, as some argue that the PAC to PRA ratio lacks specificity to be used as a screening test. They note that overreliance on the ratio as a screening test combined with a selection bias based on patients referred to hypertension specialty clinics contribute to an exaggeration of prevalence. Moreover, varying thresholds for what is considered an elevated ratio, considerable variation in laboratory assays, and lack of standardization have resulted in a broad range of prevalence estimates [44–46]. As the incidence and prevalence of the disease increase, some clinicians suggest screening all hypertensive patients for primary hyperaldosteronism, although this subject also is under much debate [47–49].

Pathologic Features

Aldosteronomas are usually solitary, unilateral, and small (typically less than 2 cm in diameter) [50]. Although adrenal tumors that hypersecrete aldosterone rarely are malignant, aldosterone-secreting adrenocortical carcinoma should be suspected in a unilateral tumor larger than 4 cm [51]. Grossly, adenomas have a characteristic golden yellow appearance on cross section due to the presence of intracytoplasmic lipid [25, 52, 53] (Fig. 27 2). Microscopically, they have large, lipid-rich clear cells. Idiopathic hyperaldosteronism, on the other hand, usually involves both adrenal glands and appears as macronodular or micronodular hyperplasia on gross and microscopic examination [54, 55]. These pathologic features, however, are not absolute, but rather represent a spectrum of

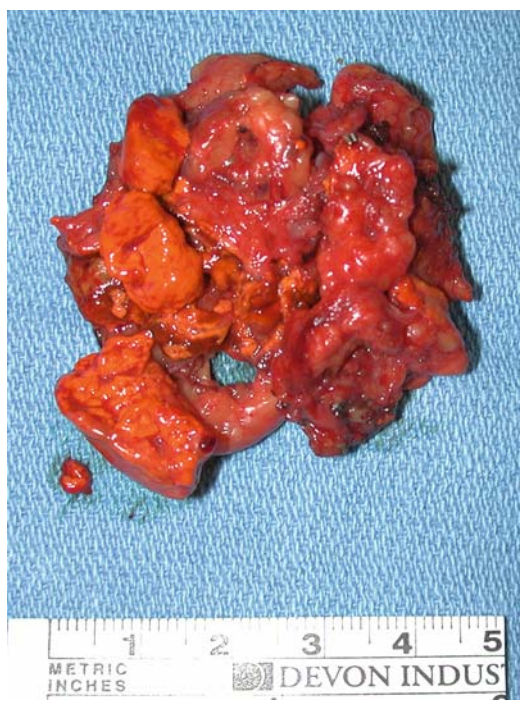

Fig. 27.2. A section through the adrenal gland reveals an aldosteronoma.

disease. Glands with adenomas, for example, often have surrounding areas of macronodular and micronodular hyperplasia [56–58]. Rare reports of unilateral hyperplasia and bilateral solitary adenomas further highlight the variable pathologic presentations of primary hyperaldosteronism that must be differentiated prior to developing a treatment strategy [59, 60].

Clinical Characteristics

Hypertension, with or without hypokalemia, results from the effect of excess aldosterone in the distal nephron as described above. The hypertension is moderate to severe and refractory to medical therapy, though malignant hypertension is rare [61–63]. Headache is common, likely secondary to hypertension. Symptoms that result from hypokalemia are nonspecific and when present include malaise, muscle weakness, paresthesias, cramps, polyuria, and polydipsia. Tetany and paralysis are rare occurrences [63]. Peripheral edema also is rare despite expanded extracellular fluid volume due to "aldosterone escape," a phenomenon in which mechanisms involving atrial natriuretic peptide and pressure natriuresis counteract the sodium-retaining effects of excess aldosterone and return the extracellular fluid volume to a steady state [64–66]. Hyperaldosteronism also induces significant cardiac and metabolic alterations including left ventricular hypertrophy, which leads to an increased risk of myocardial infarction and stroke, and insulin resistance, which leads to glucose intolerance and increased body mass index (BMI) [67–70]. These deleterious effects are mediated in part by aldosterone receptors in the heart, brain, and blood vessels throughout the body [71]. Normalization of circulating aldosterone levels in addition to control of hypertension and hypokalemia thus is a vital part of the management plan for all patients with primary hyperaldosteronism [8].

Diagnosis

Refractory hypertension and hypokalemia should raise suspicion of hyperaldosteronism. Hypokalemia, however, is not an obligatory finding. Indeed, recent studies have consistently found that hypokalemia occurs in a minority of patients with primary hyperaldosteronism, and many researchers now advocate screening for primary hyperaldosteronism whether or not hypokalemia is present [32, 37, 72, 73]. When primary hyperaldosteronism is suspected, it is necessary first to establish the presence of hyperaldosteronism biochemically and then to distinguish surgically correctable unilateral disease from medically treatable bilateral disease.

Biochemical Diagnosis

Elevated aldosterone levels with suppressed renin levels are characteristic biochemical features of primary hyperaldosteronism. An initial test that determines the PAC to PRA ratio by measuring PAC (in ng/dL) and PRA (in ng/mL/hr) has been recommended in several studies to screen for patients with primary hyperaldosteronism [44, 74–76]. Elevated PAC levels in combination with an elevated PAC:PRA ratio further improve the screening strategy [77]. While different authors report variable cutoff values for both the PAC:PRA ratio and the PAC level, a ratio greater than 20–30 in the setting of a PAC level greater than 15–20 ng/dL generally are reliable criteria to secure the diagnosis [10, 78–80].

Certain medications that affect the renin-angiotensin-aldosterone axis may confound the results of the PAC:PRA screening test [26, 38, 39, 42]. Spironolactone, an aldosterone antagonist, renders the test uninterpretable. Estrogens likewise confuse the results as they increase angiotensinogen and consequently increase PACs [23]. Both should be discontinued 6 weeks before performing the workup. Other medications including diuretics, ACE inhibitors, and vasodilators also should be stopped 4–6 weeks prior [81]. Control of hypertension still is necessary, however, and peripheral alpha-adrenergic blockers, beta-blockers, and calcium-channel blockers are the preferred agents during evaluation.

An increased PAC:PRA ratio alone does not make the diagnosis of primary hyperaldosteronism. A suppression test should be performed to demonstrate that the aldosterone secretion is inappropriate for a high-sodium diet and not normally suppressible. Between 30 and 50% of patients with a positive PAC:PRA ratio will have appropriate aldosterone levels that are normally

suppressed by confirmatory testing [82]. Failure to suppress aldosterone production with a sodium challenge (i.e., saline suppression test) can confirm a suspected diagnosis of primary hyperaldosteronism. The saline suppression test can be performed with either intravenous or oral sodium loading. For intravenous loading, 2 l of 0.9% normal saline are infused over 4 h in patients who have consumed a low-sodium diet for three days [26, 83]. For oral loading, the patient consumes a high-sodium diet for three days supplemented with sodium chloride tablets. After the sodium challenge, a plasma aldosterone level is measured and a 24-h urine sample is collected for aldosterone and sodium levels. Failure to suppress PAC below 10 ng/ml and urinary aldosterone secretion of greater than 12 ug/24 h with urinary sodium excretion greater than 200 mEq/24 h suggest primary hyperaldosteronism [26, 82, 84].

Captopril, an ACE inhibitor, and fludrocortisone, a mineralocorticoid, also have been used to test the suppressibility of aldosterone production [85, 86]. The usefulness of the captopril suppression test is debatable [87]. While many authors consider the fludrocortisone suppression test (FST) to be the most reliable confirmatory test, it is complex and costly. FST risks severe hypokalemia that requires hospitalization for close monitoring, which is both time-consuming and expensive, thus limiting its usefulness [82].

Differentiating Unilateral and Bilateral Disease

Once the diagnosis of primary hyperaldosteronism has been made, it is necessary to distinguish between unilateral and bilateral adrenal disease to guide treatment. Patients with aldosteronomas generally are younger, have more severe hypertension, more profound hypokalemia, and higher plasma and urinary aldosterone levels than patients with idiopathic hyperaldosteronism [26, 79]. These clinical characteristics are unreliable, however, and further testing is necessary to predict unilateral versus bilateral adrenal disease [8].

The postural stimulation test, based on the differential regulatory mechanisms of the two conditions, is one noninvasive method of predicting aldosterone-producing adenoma versus idiopathic hyperaldosteronism [88, 89]. Aldosteronomas are unaffected by feedback from the renin–angiotensin system, but remain sensitive to ACTH. Plasma aldosterone levels, therefore, fall with ACTH and cortisol levels as the day progresses in patients in an upright position. PRA remains suppressed. In contrast, idiopathic hyperaldosteronism demonstrates enhanced sensitivity to small changes in the renin–angiotensin system, but is relatively unaffected by ACTH. Plasma aldosterone levels in these patients, therefore, rise with the relative increase in PRA that occurs in the upright position. False-negative results of the postural stimulation test, however, are reported in the literature [50, 56]. Stress during the test likely can stimulate ACTH release and elevate PAC, thus confounding the results.

Measurement of plasma 18-hydrocorticosterone (18-OHB) concentration also has been used to differentiate between aldosterone-producing adenoma and idiopathic hyperaldosteronism [90]. An aldosterone-producing adenoma typically is associated with a plasma 18-OHB level greater than 100 ng/dl. The assay to measure 18-OHB, however, is not commonly available, and its reported accuracy of about 80% limits its usefulness [50, 91].

Localization

Differentiation between the unilateral and the bilateral forms of primary hyperaldosteronism thus cannot be made convincingly with the currently available biochemical studies. Localization studies usually are necessary and, in combination with the aforementioned tests, can greatly improve diagnostic accuracy. Actually visualizing an adrenal tumor by radiography or detecting unilateral excess aldosterone production by adrenal venous sampling helps separate patients who may benefit from adrenalectomy from those who should be managed medically.

High-resolution, thin-section computed tomography (CT) scan is the preferred initial imaging modality for a suspected aldosterone-producing adrenocortical adenoma. The sensitivity of modern scanners approaches 90% with thin cut (i.e., 5 mm or less) adrenal protocols [92, 93]. Most aldosterone-producing adenomas that cause clinically significant hyperaldosteronism can be seen on CT as hypodense lesions that measure 0.5–2.0 cm in diameter [94, 95] (Fig. 27.3). The

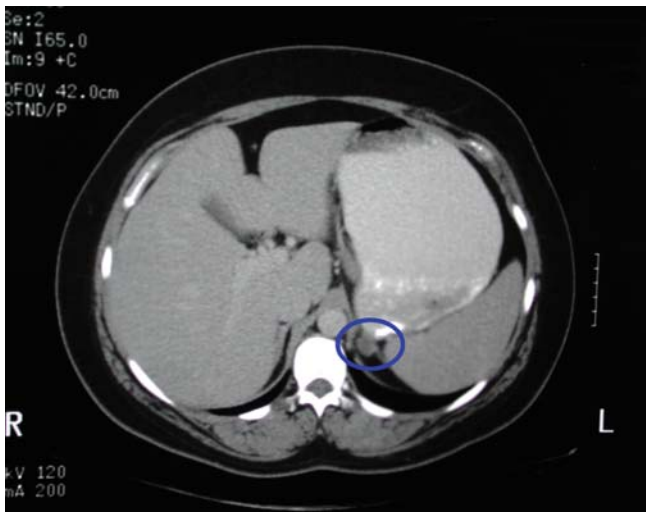

Fig. 27.3. A CT scan with thin cuts through the adrenal glands shows an aldosterone-producing adenoma on the left.

presence of a unilateral lesion measuring 1–2 cm with a normal contralateral adrenal gland on CT scan is strong evidence for an adenoma and further localization is likely unnecessary [96]. Small aldosteronomas (<0.5 cm), however, can be missed by CT scan, leading to a misdiagnosis of adrenal hyperplasia in a patient with clinical hyperaldosteronism. Moreover, aldosteronomas can reside amid nonfunctional adenomas in one or both glands, appear as multinodularity or bilateral lesions on CT, and thus may be mistaken for hyperplasia [97, 98]. Conversely, hyperplasia can appear as a small lesion on CT and be mistaken for an aldosteronoma. The radiographic diagnosis and localization of an aldosterone-producing adenoma, therefore, cannot be definitive unless the CT scan clearly demonstrates a unilateral 1- to 2-cm lesion with a normal contralateral adrenal gland. CT findings of a unilateral lesion less than 1 cm or greater than 2 cm, unilateral adrenal thickening, bilateral adrenal nodularity, or bilateral normal adrenal glands warrant additional testing to differentiate between possible aldosterone-producing adenomas and hyperplasia [96, 99, 100].

Magnetic resonance imaging (MRI) is another imaging option. While costly, it is useful for imaging the adrenal glands in pregnant patients, iodine allergic patients, or when CT scan is otherwise contraindicated [101, 102] (Fig. 27 4). Adrenal scintigraphy with ^{131}I-6beta-iodomethyl-19-norcholesterol (NP-59) in conjunction with dexamethasone suppression has been used to diagnose and locate overactive adrenal glands when CT results are equivocal. Lateralization of NP-59 uptake is primarily dependent on tumor size, however, and is less accurate for small lesions. Additionally, NP-59 scanning requires an involved set up and significant time to block thyroid uptake of radioiodine, prohibiting its widespread use [103]. At the time of this publication, NP-59 is no longer available in the USA.

When successful, adrenal venous sampling remains the most accurate method for differentiating between unilateral aldosteronoma and idiopathic hyperaldosteronism [93, 98, 104].

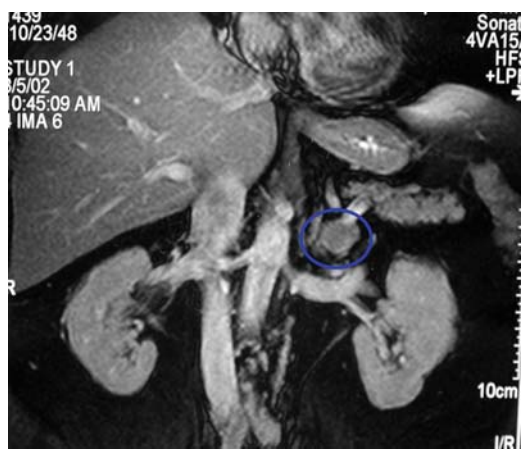

Fig. 27.4. An MRI demonstrates a left aldosterone-producing adrenocortical adenoma.

While some authors consider it a routine part of the workup for primary hyperaldosteronism, others feel it should be reserved for patients in whom imaging is inconclusive [72, 105–107]. Arguments for its routine use cite that as many as one third of patients thought to have a unilateral lesion on imaging studies will have bilateral adrenal hyperplasia on adrenal venous sampling. Against its routine use are the facts that it is invasive and has resulted in complications such as thrombosis and rupture of the adrenal veins, bleeding, and adrenal infarction. Moreover, it is technically difficult and failure to cannulate the adrenal veins, especially on the right, is common [106]. In the hands of an experienced angiographer, however, the successful cannulation rate is approximately 90% [93, 100, 108, 109].

Selective venous sampling involves obtaining plasma levels of cortisol and aldosterone from both adrenal veins and the inferior vena cava. Cortisol and aldosterone levels are measured at each of these points before and after administration of ACTH. ACTH infusion minimizes any fluctuations due to episodic changes in aldosterone secretion that might be caused by stress-induced endogenous ACTH release [100, 106]. When performing selective venous sampling, the two main goals are to (1) confirm successful cannulation of the adrenal veins and (2) determine if there is lateralization of aldosterone hypersecretion. To confirm proper cannulation of the adrenal veins, cortisol levels from the adrenal vein samples are compared to the vena cava sample on the theory that the cortisol levels will dilute and thus decrease at locations further from the adrenal gland. If there is a twofold greater concentration of cortisol in each adrenal vein when compared to the vena cava, then successful cannulation is assured and determination of laterality can be conducted. In addition, measuring cortisol levels helps to assure that specimens have not been mislabeled since cortisol levels should be lower in the left adrenal vein when compared with the right adrenal vein due to dilution from the phrenic vein. The comparison of the aldosterone-to-cortisol ratio between the right and the left adrenal vein samples determines whether unilateral or bilateral hypersecretion of aldosterone is present. Although the limit is controversial, an aldosterone-to-cortisol ratio in one adrenal vein that is four times greater than that obtained from the contralateral vein is considered indicative of a unilateral aldosterone-producing tumor. This fourfold greater ratio is predictive of a unilateral lesion in more than 90% of cases [100]. Minimal difference in the ratios between the two sides suggests bilateral aldosterone hypersecretion.

Treatment

The goal of treatment, whether medical or surgical, is to prevent the morbidity and mortality of the hypertension, hypokalemia, and cardiometabolic alterations associated with aldosterone excess [9]. Patients with clinical primary hyperaldosteronism and a unilateral source of excess aldosterone secretion should be considered for unilateral adrenalectomy. Patients with bilateral sources of excess aldosterone secretion or those who are poor surgical candidates should undergo medical therapy [110–112] (Table 27.2).

Surgical

Causes of hyperaldosteronism that respond to adrenalectomy include unilateral adrenocortical adenoma, unilateral adrenal hyperplasia, unilateral adrenocortical carcinoma, and familial hyperaldosteronism type 2. Adrenalectomy for idiopathic hyperaldosteronism seldom corrects the hypertension and is not indicated [50, 79, 113, 114]. Adrenalectomy for bilateral aldosterone-producing tumors also is not indicated. Bilateral aldosterone-producing tumors are rare, and the resultant adrenal insufficiency from adrenalectomy may be more difficult to manage medically than the hypertension [115].

The traditional approach for adrenalectomy is via an open flank or posterior incision. Most

Table 27.2. Treatment for primary hyperaldosteronism

Surgical
Aldosterone-producing adrenocortical adenoma
Aldosterone-producing adrenocortical carcinoma
Unilateral adrenal hyperplasia
Familial hyperaldosteronism, Type II
Medical
Idiopathic bilateral adrenal hyperplasia
Familial hyperaldosteronism, Type I

authors still recommend open adrenalectomy for suspected adrenocortical carcinoma as these cancers usually are large and advanced when discovered [116–119]. Laparoscopic unilateral adrenalectomy, however, has emerged as a safe, effective, and optimal surgical treatment for the aforementioned subtypes of primary hyperaldosteronism [120–124]. Although operative time and complications may not be significantly different from open adrenalectomy, advantages include smaller wounds, less postoperative pain, and shorter hospital stays [125, 126]. Most patients are able to leave the hospital within 48 h of a laparoscopic adrenalectomy [127, 128].

Preoperative treatment with spironolactone, a competitive aldosterone antagonist, reduces surgical risks by helping to control blood pressure and correct hypokalemia. Studies have shown that control of blood pressure by spironolactone before surgery is a good predictor of successful treatment of hypertension after surgery [25, 129, 130]. Preoperative aldosterone receptor blockade also reduces the risk of postoperative hypoaldosteronism by reactivating the aldosterone-suppressed renin–angiotensin–aldosterone system and allowing the contralateral adrenal gland to begin functioning normally again [8]. Postoperative postural hypotension and hyperkalemia may be signs of postoperative hypoaldosteronism. Treatment involves adequate sodium intake and/or short-term fludrocortisone replacement.

Medical

The indications for medical therapy include idiopathic hyperaldosteronism, glucocorticoid-suppressible hyperaldosteronism, and primary hyperaldosteronism of whatever etiology in patients who are poor surgical candidates. Idiopathic hyperaldosteronism and hyperaldosteronism in high-risk surgical candidates both respond to management with an aldosterone antagonist, whereas glucocorticoid-suppressible hyperaldosteronism responds to exogenous steroid administration. Spironolactone is the mineralocorticoid receptor antagonist of choice and is effective in controlling hypertension and hypokalemia, though it is not without side effects [112, 131]. As a competitive mineralocorticoid receptor blocker, spironolactone binds androgen and progesterone receptors as well as aldosterone receptors and may cause generalized gastrointestinal upset, breast tenderness, and menstrual irregularities in women, and decreased libido, impotence, and gynecomastia in men [111, 112, 132]. Eplerenone, a highly selective mineralocorticoid receptor antagonist, has less binding affinity to androgen and progesterone receptors and thus is associated with fewer side effects [133, 134]. It is more expensive, however, and randomized, placebo-controlled trials are needed to evaluate its efficacy relative to spironolactone. Dexamethasone is used to suppress ACTH production and control aldosterone excess in glucocorticoid-suppressible hyperaldosteronism. It is administered in small doses to avoid signs and symptoms of Cushing's syndrome [12].

Postoperative Outcomes

Excision of an aldosterone-producing adenoma normalizes potassium levels in more than 95% of patients almost immediately and improves hypertension in over 75% within 1 month of surgery [50, 79, 109, 135]. Of those patients with improvement in hypertension, approximately one third will require no antihypertensive medications and two thirds will require fewer antihypertensive medications than before surgery. Long-term cure of hypertension, however, ranges from 30 to 60% in reported series possibly due to concurrent underlying essential hypertension and/or atherosclerosis and end-organ damage from the prior long-standing presence of hypertension and aldosterone excess [9, 129, 130, 136, 137]. The association between increasing age and longer duration of hypertension with persistent postoperative hypertension further supports the idea that persistent hypertension is likely the result of the reduced ability to reverse chronic pathologic vascular changes [56, 138, 139]. Early diagnosis and treatment thus may result in better outcomes.

Conclusion

Primary hyperaldosteronism is a potentially curable cause of hypertension. Refractory hypertension with or without hypokalemia

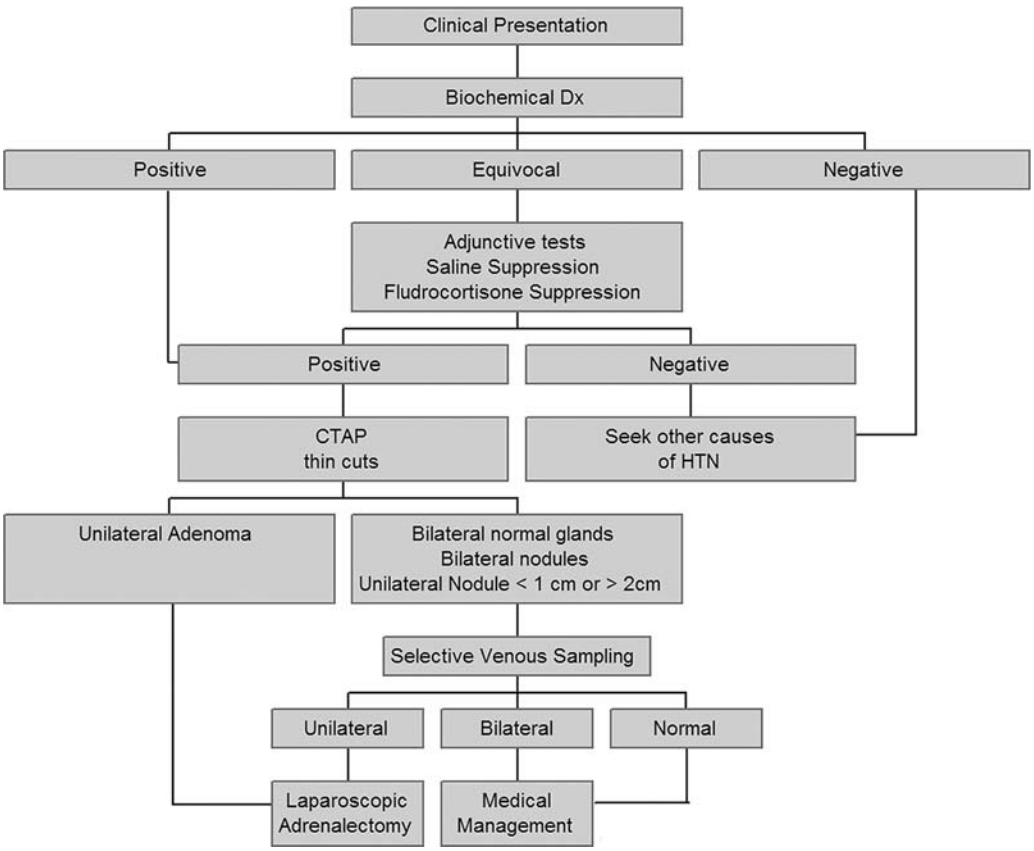

Fig. 27.5. General algorithm for diagnosing and treating primary hyperaldosteronism.

should prompt a workup for primary hyperaldosteronism. Once the diagnosis is made, it is crucial to differentiate between unilateral and bilateral sources of aldosterone excess. This distinction is important for selecting patients who may benefit from surgical versus medical therapy (Fig. 27.5). Laparoscopic unilateral adrenalectomy is the recommended surgical approach for aldosteronoma while aldosterone receptor antagonist therapy is the recommended medical treatment for idiopathic hyperaldosteronism. Adrenalectomy normalizes hypokalemia in virtually all patients and significantly improves hypertension in about 60% of patients while also protecting against the harmful cardiometabolic effects associated with aldosterone excess.

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28

Cushing's Disease and Syndrome

Brian Hung-Hin Lang and Chung-Yau Lo

Introduction

In 1932, Harvey W. Cushing first described a disease entity characterized by muscular weakness, obesity, abdominal striae, diabetes, and arterial hypertension from a specific pituitary cause of hypercortisolism, which is known as Cushing's disease nowadays. With an increased understanding of the different etiological causes of hypercortisolism, Cushing's syndrome is recognized or represents as a distinct disease entity with a complex of symptoms and signs caused by prolonged and inappropriate exposure to excess glucocorticoids.

Epidemiology and Etiology

Cushing's syndrome is considered a rare disease as its incidence ranges from 0.7 to 2.4 per million per year [1]. Although the diagnosis can be readily made for patients presenting with classical clinical features (i.e., overt Cushing's syndrome), it is now realized that majority of patients suffer from a more subtle or subclinical form of Cushing's syndrome [2]. Patients with subclinical Cushing's syndrome have at least two biochemical abnormalities in the hypothalamo–pituitary–adrenal axis but lack the classic clinical symptoms and signs of hypercortisolism [2, 3]. However, the prevalence of obesity, hypertension, and type II diabetes are high, and surgical intervention has been shown to improve these metabolic abnormalities [2, 3]. If obese patients with poorly controlled type II diabetes mellitus and hypertension are screened for Cushing's syndrome, the reported prevalence ranges from 2 to 5% [4, 5].

Cushing's syndrome can cause significant long-term morbidity and mortality. In the early 1950s, a study on natural history of Cushing's syndrome showed that untreated patients had a 5-year survival of only 50% [6]. A more recent study confirmed that those with incompletely controlled Cushing's syndrome had up to 11-fold increase in mortality when compared to the national average over the long term [1]. Despite these findings, long-term prospective studies evaluating the outcome of patients with subclinical Cushing's syndrome are lacking and the overall benefit of surgical intervention for adrenal incidentaloma with subclinical Cushing's syndrome remains somewhat controversial [2, 3, 7]. In addition, Cushing's syndrome is a rare condition that resembles many of the phenotypic features of modern life such as obesity, hypertension and depression, the cost effectiveness of screening for these high-risk groups alone based on phenotypic features or the wider population remains doubtful [8–12].

By far, the most common cause of Cushing's syndrome is the prolonged exogenous administration of excess amount of glucocorticoids during the treatment of various diseases. Therefore, by taking a detailed medication history, the clinical suspicion can frequently be confirmed [11]. Endogenous causes of hypercortisolism are

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Table 28.1. Underlying causes of Cushing's syndrome

	Proportion (%)
ACTH-dependent causes	80–85
Cushing's disease	70
Ectopic ACTH syndrome	10
Unknown source of ACTH	5
ACTH-independent causes	Up to 20
Adrenal adenoma	10
Adrenal carcinoma	5
Macronodular adrenal hyperplasia	<2
Primary pigmented nodular adrenal disease	<2
McCune–Albright syndrome	<2

usually divided into the adrenocorticotrophin (ACTH)-dependent and ACTH-independent groups (Table 28.1). The ACTH-dependent group accounts for 80–85% of all cases of endogenous hypercortisolism, and within this group, 80 and 20% can be attributed to pituitary (Cushing's disease) and ectopic sources of ACTH respectively [13, 14]. Small-cell bronchogenic carcinoma followed by bronchial or thymic carcinoids, and other neuroendocrine tumors such as pheochromocytoma, pancreatic neuroendocrine tumors, and gastrointestinal carcinoids are common causes of ectopic ACTH syndromes. Patients suffering from small-cell carcinoma of lung frequently manifest diagnostic paraneoplastic wasting syndrome while, for other ectopic sources of ACTH, the clinical presentation would be difficult to distinguish from Cushing's disease. ACTH-independent Cushing's syndrome is most commonly due to a unilateral functional adrenal adenoma, accounting for approximately 60% of cases while adrenal carcinoma accounts for the remaining cases. Bilateral adrenal masses such as ACTH-independent macronodular adrenal hyperplasia (AIMAH) and primary pigmented nodular adrenal disease (PPNAD) are, albeit rarely, ACTH-independent causes of Cushing's syndrome.

Clinical Features

A wide variety of symptoms and signs result from the metabolic effects of excessive glucocorticoid production (Fig. 28.1). Table 28.2 summarizes the clinical manifestations of

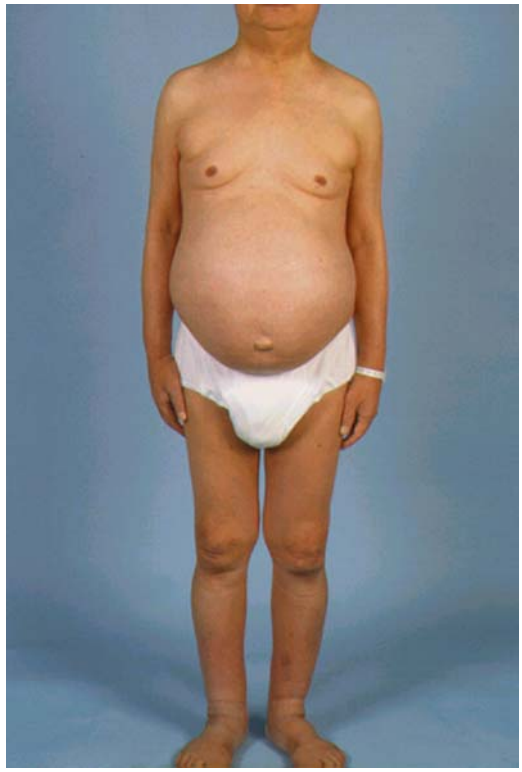

Fig. 28.1. Characteristic appearance of a patient with Cushing's syndrome including moon face, truncal obesity, proximal muscle wasting, and buffalo hump.

Table 28.2. Clinical manifestations of Cushing's syndrome

Signs and symptoms	%
Obesity or weight gain	95
Facial plethora	90
Rounded face	90
Decreased libido	90
Thin skin	85
Decreased linear growth in children	70–80
Menstrual irregularity	80
Hypertension	75
Hirsutism	75
Depression/emotional lability	70
Easy bruising	65
Glucose intolerance	60
Weakness	60
Osteopenia or fracture	50
Nephrolithiasis	50

Cushing's syndrome. However, some of these clinical features are neither specific nor frequently apparent at presentation. Diagnosis is challenging and depends on a high index of suspicion. In addition, patients with other metabolic syndromes frequently share various similar, if not identical, clinical features [11]. Signs of protein wasting including the presence of thin skin in the young, easy bruising, and proximal muscle weakness could more reliably distinguish Cushing's from metabolic syndrome [11]. In contrast, obesity and decreased linear growth are more common in children with Cushing's syndrome [15, 16]. Patients typically have truncal obesity with "moon face" (Fig. 28.2) and fullness of the supraclavicular fat pads ("buffalo hump"). There are also some differences in presentation between men and women. Purplish abdominal cutaneous striae, muscle atrophy, osteoporosis, and kidney stones more common in male patients [17]. Although gonadal or sexual dysfunction is common in both sexes, oligomenorrhea is a common presentation in premenopausal women and may occur before other manifestations. Renal stones are present in about 50% of patients [18]. More than 70% of patients can present with psychiatric symptoms ranging from anxiety to frank psychosis. Impairment of short-term memory or cognitive function is common [19] and is frequently associated with a reduction in apparent brain volume that slowly reverses after correction of hypercortisolism [20]. However, quality of life might remain impaired even after the resolution of hypercortisolism [21–23].

Metabolic manifestations are commonly presented as laboratory abnormalities including hyperlipidiemia, impaired glucose tolerance test or diabetes, lymphocytopenia, eosinopenia, high hematocrit, and hemoglobulin as well as hypercalciuria. Because of the precision of laboratory and imaging studies, Cushing's syndrome is increasingly diagnosed earlier during its course and florid clinical or laboratory manifestations are becoming increasingly less apparent [11].

Investigations

Biochemical Evaluations

In principle, clinical suspicion of Cushing's syndrome should be confirmed by biochemical evaluations. On the other hand, incidentally

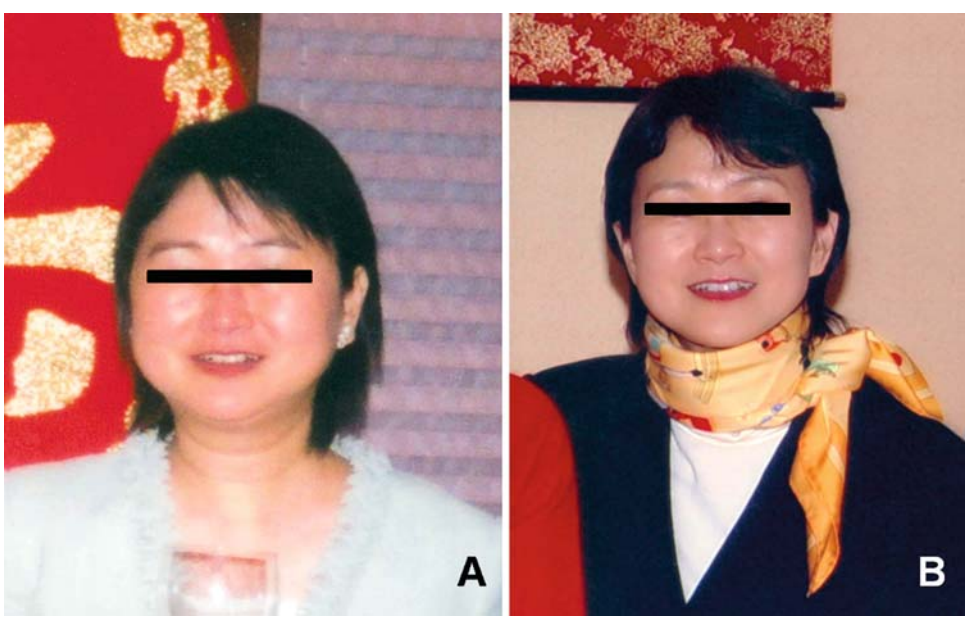

Fig. 28.2. Facial appearance (moon face) of a young woman with Cushing's syndrome due to an adrenal adenoma 1 year before (**A**) and after surgical treatment (**B**).

detected adrenal mass should be evaluated for potential subclinical hypercortisolism. In addition, high-risk patient groups such as those with poorly controlled diabetes and/or hypertension with overlapping clinical features should be subjected to routine biochemical screening. However, no single biochemical test is perfect for screening and several tests are usually necessary [8]. The currently accepted screening tests include 24 h urinary free cortisol, overnight/low-dose dexamethasone-suppression test and assessment of late-night salivary cortisol [7].

Measurement of urinary cortisol is a direct measurement of circulating free or biologically active cortisol. Excess circulating cortisol saturates the corticosteroid-binding globulins and is excreted in urine as free cortisol. Unlike plasma cortisol, it is unaffected by factors that influence corticosteroid-binding globulins [24, 25]. Up to three 24 h urine collections should be performed to exclude intermittent hypercortisolism. Values greater than threefold the upper limit of normal are diagnostic [8] while milder elevation can be found in conditions such as chronic anxiety or major depression states (stimulate glucocorticoid secretion), chronic intake of drugs including barbiturates, phenytoin, rifampicin or alcohol (accelerate cortisol metabolism), and obesity as well as high estrogen states [10]. A normal value of urine cortisol (<135 nmol/24 h) excludes the diagnosis of Cushing's syndrome with a high degree of accuracy. However, to avoid a falsely low result, the total urinary volume and urine creatinine should be measured in all samples to ensure completeness of collection or urinary cortisol value adjusted with the creatinine clearance [8].

Both overnight and 48-h/low-dose dexamethasone-suppression tests are used widely. The former test involves giving 1 mg dexamethasone at 23:00 or midnight and then checking the serum concentration of cortisol at 08:00–09:00 the next morning. The latter test involves giving dexamethasone 0.5 mg every 6 hourly for 2 days and checking the cortisol level both at the start and at the end of the 48-h test. To exclude Cushing's syndrome, the serum concentration of cortisol should be suppressed to less than 50 nmol/l (2 μg/dl) [26, 27]. The overnight test is a simple screening test but a false-positive rate of up to 30% has been reported in healthy individuals [28]. Patients with malabsorption or increased hepatic clearance of dexamethasone (e.g., those taking carbamazepine, phenytoin, phenobarbitol, or rifampicin) are more likely to have false-positive results [29]. The 48-h or low-dose dexamethasone test has a higher specificity and should be performed to confirm a positive overnight screening test [11]. Some 3–8% of patients with Cushing's disease may retain sensitivity to dexamethasone and show suppression of serum cortisol on either test [30, 31].

Late-night salivary cortisol measurement is a recently introduced test with promising role for screening of Cushing's syndrome. Cortisol concentration in saliva highly correlates with free plasma cortisol and is independent of salivary flow rate [32, 33]. Late night (23:00) salivary cortisol is a simple way to screen for Cushing's syndrome and has become increasingly used with a relatively high sensitivity and specificity of 95–98% [11]. It is particularly useful in investigating patients with cyclical Cushing's syndrome by repeated measurements of evening cortisol over time [34].

Evaluation of the Etiological Causes

Once the diagnosis of hypercortisolism has been confirmed biochemically with hormonal evaluations, the underlying cause should be sought. Figure 28.3 shows the commonly adopted evaluation algorithm in establishing the underlying cause of Cushing's syndrome. Measurement of plasma ACTH concentration should be considered as the first step to provide potential important information. It is important that when taking blood for ACTH, the plasma should be separated rapidly and stored at –40°C to avoid degradation and a falsely low result. Undetectable or low ACTH concentrations less than 2 pmol/l (10 pg/ml) indicate ACTH-independent Cushing's syndrome and adrenal causes should be sought. On the other hand, when ACTH concentrations are grossly elevated to greater than 4 pmol/l (20 pg/ml), ACTH-independent causes, Cushing's disease or ectopic ACTH production, are likely. Values between these two limits need careful interpretation because patients with Cushing's disease and adrenal pathologies might give rise to intermediate values.

Measurement of ACTH could not frequently arrive at the diagnosis and other hormonal evaluations are frequently required. When

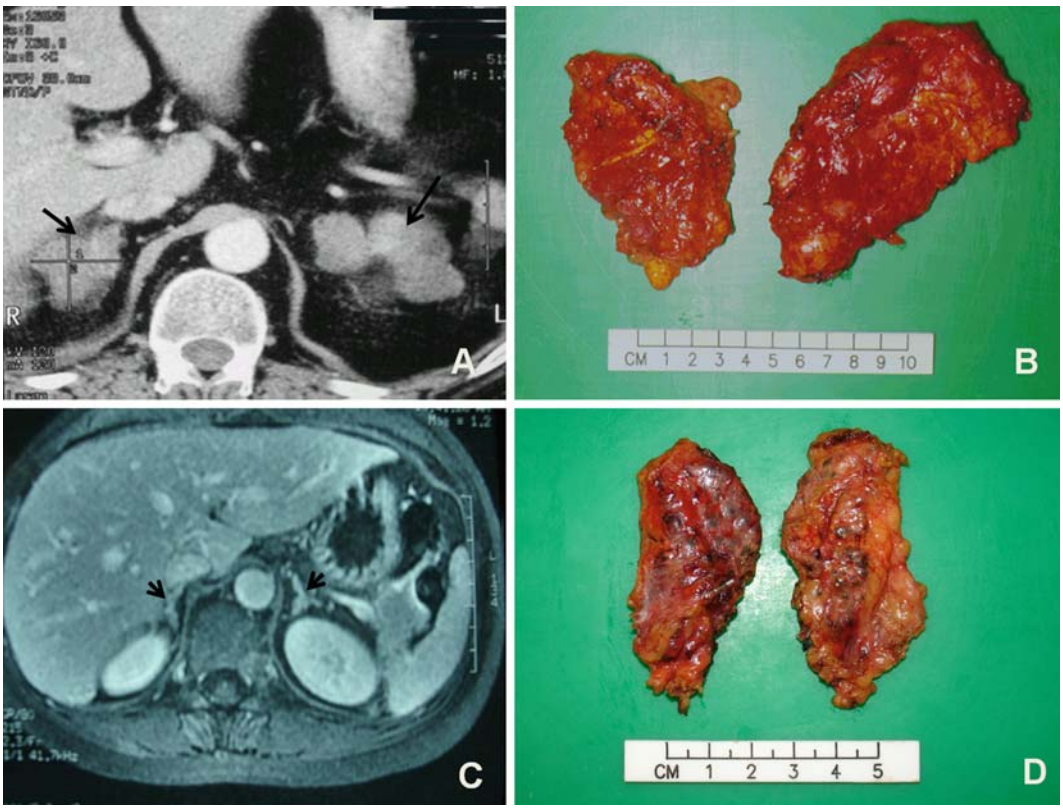

Fig. 28.3. CT scan of a patient with bilateral macronodular adrenal hyperplasia (**A**) and the bilateral laparoscopic adrenalectomy specimens (**B**); MRI of a patient with primary pigmented nodular adrenal hyperplasia (**C**) and the bilateral laparoscopic adrenalectomy specimens (**D**).

ACTH-dependent causes of Cushing's syndrome are considered, distinguishing pituitary from nonpituitary sources of excess ACTH can be extremely challenging, but nevertheless, the distinction is important to guide definitive treatment [11, 35]. Biochemical assessment is more useful than imaging for differentiating between pituitary and nonpituitary cause because up to 40% of proven Cushing's disease have normal pituitary magnetic resonance imaging (MRI) whereas those with nonpituitary cause could have a pituitary incidentaloma (although rarely larger than 6 mm in size) [36]. The high-dose dexamethasone-suppression test (in the form of 2-mg dose given every 6 h or one single dose of 8-mg dose at 23:00) could partially suppress ACTH secretion from most pituitary adenomas (about 80%) and not for ectopic ACTH tumors. A suppression of cortisol of more than 50% of basal level implies a positive test result. However, occasionally benign tumors such as the carcinoid tumors of bronchus or thymus may still have a suppressed cortisol.

For patients with equivocal ACTH and high-dose dexamethasone-suppression test results, the corticotrophin-releasing hormone (CRH) stimulation test might also be useful because most pituitary tumors and only a few ectopic ACTH-secreting tumors respond to CRH administration. In this test, an intravenous bolus of either 1 μg/kg or more usually 100 μg is given to stimulate the corticotrope tumor cells in the pituitary gland to release ACTH, which, in turn, will raise the serum cortisol concentration. There is no consensus on the criteria adopted for interpreting a positive response to CRH stimulation in the test. Variability in the interpretation depends on the type of CRH used, the biochemical parameters measured (35–50%

increase of ACTH above baseline vs 14–20% increase of cortisol), and the evaluated time points (ACTH, 15–30 min vs cortisol, 15–45 min) after CRH injection [36–38]. However, because some ectopic ACTH-producing tumors also show positive response to CRH stimulation, the specificity of the test cannot reach 100% despite increasing the cutoff level of the response [8].

Localization

If ACTH-dependent Cushing's syndrome is suspected based on ACTH measurement but the source of ACTH is nondiagnostic based on the high-dose dexamethasone-suppression and CRH stimulation tests, the next investigation of choice is the pituitary MRI. If both the clinical presentation and the dynamic biochemical studies are compatible with ACTH-dependent Cushing's syndrome, an isolated lesion of 6 mm or more on pituitary MRI is almost diagnostic of Cushing's disease. However, up to 40% of patients with proven Cushing's disease have normal pituitary MRI scans and up to 10% of the normal population has a pituitary incidentaloma (usually 5 mm or less). In these patients, bilateral selective inferior petrosal sinus venous sampling to compare the gradient of ACTH with the periphery is the most reliable means of discriminating between pituitary and nonpituitary sources of ACTH. However, venous sampling is a highly operator-dependent, technically demanding, skilled, and invasive technique. A greater than 50% increase in central corticotrophin level compared with basal or a central-to-peripheral ratio of more than 2–3:1 is consistent with Cushing's disease when stimulated by CRH with a reported sensitivity and specificity of 94% and 95–100%, respectively [39–43]. In one study, 2 of 179 patients noted to have responses consistent with Cushing's disease were ultimately confirmed to have ectopic ACTH syndrome [44]. However, venous sampling has only 70% accuracy in lateralizing the source of ACTH within the pituitary gland in adults although the accuracy is much greater for children [8, 10, 45]. Direct sampling from the cavernous sinuses does not improve the accuracy. On the other hand, sampling from the internal jugular veins has been proposed as a simplified procedure but is associated with a lower sensitivity and specificity [46].

On the other hand, when ACTH-independent Cushing's syndrome causes such as adrenal adenoma, adrenocortical carcinoma, or AIMAH are considered, the anatomical cause is invariably visible on fine-cut CT scan or MRI. In PPNAD, the adrenal glands would appear normal in shape and size (Fig. 28.3). Since PPNAD is associated with Carney's complex, other features of the complex such as lentigines or myxomas might help with the diagnosis. In ACTH-dependent Cushing's syndrome, the adrenals may sometimes appear slightly enlarged and could cause some diagnostic confusion with a primary adrenal cause. In 30% of Cushing's disease, the adrenals appear normal whereas in ectopic ACTH syndrome, the adrenals are homogeneously enlarged [47]. When ectopic ACTH Cushing's syndrome is suspected, axial imaging with thin-cut multislice CT of the thorax and abdomen has a high detection rate for the primary tumors [13, 14, 48]. Patients harboring small neuroendocrine tumors which express somatostatin receptors can be localized by somatostatin-receptor scintigraphy. Although the scintigraphy may confirm functionality for a lesion seen on axial CT scan, its ability to disclose a truly occult tumor invisible on CT is limited [49, 50]. PET with ^{18}FDG may be of some benefit in locating ectopic ACTH-secreting neuroendocrine tumors, although these tumors are usually of low metabolic activity [51, 52]. Use of ^{11}C-5-hydroxytryptophan has been proposed as a universal imaging technique for neuroendocrine tumors but further evaluation is needed before its usefulness can be established [53]. Figure 28.4 summarizes the commonly adopted evaluation protocol and management algorithm for patients with biochemical confirmed endogenous hypercortisolism.

Management

Medications

Although the primary therapy for Cushing's syndrome is surgical, medical treatment is frequently recommended for perioperative control of hypercortisolism or when surgery is not feasible. Metyrapone, ketoconazole, and mitotane have all been demonstrated to lower cortisol by inhibiting synthesis and secretion of the adrenal gland [11, 54]. The former two drugs are enzyme

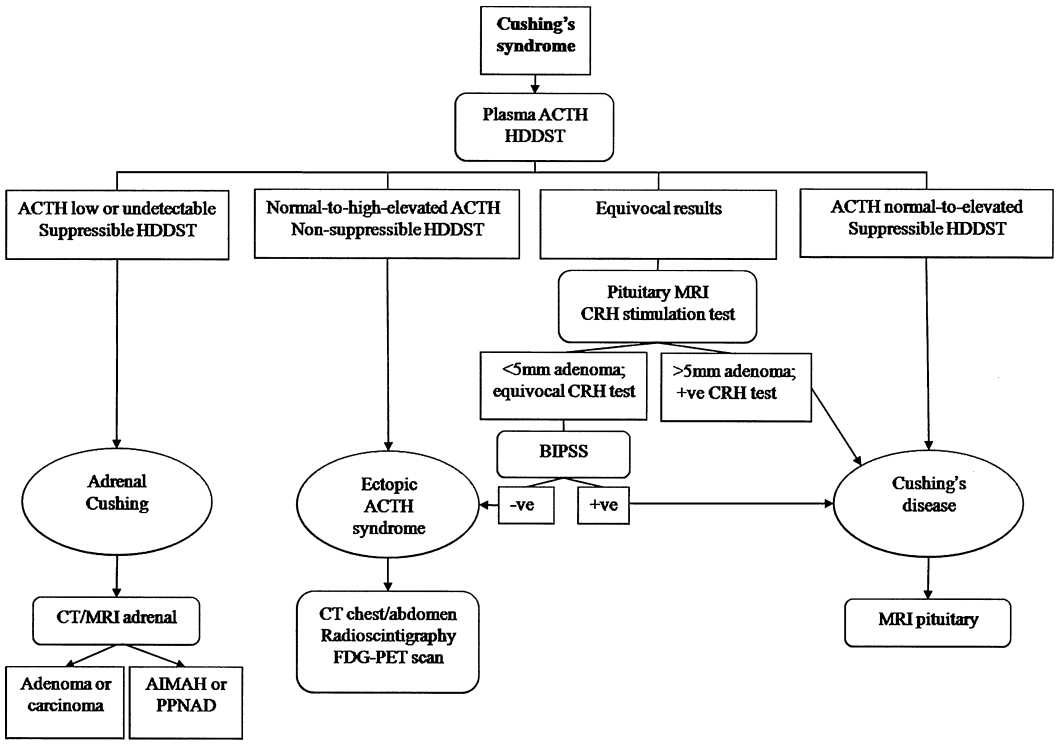

Fig. 28.4. Proposed algorithm for the workup and management protocol of patients with confirm endogenous hypercortisolism (Abbreviations: CRH = corticotrophin-releasing hormone; AIMAH = ACTH-independent macronodular adrenal hyperplasia; PPNAD = primary pigmented nodular adrenal disease; BIPSS = bilateral inferior petrosal sinus venous sampling; HDDST = high-dose dexamethasone-suppression test).

inhibitors and have rapid onset of action, but are less effective for Cushing's disease due to ACTH oversecretion (the so-called escape phenomenon) [11]. They are not effective for long-term control but are often used before or as an adjunct after surgery. Mitotane (p'DDD) acts as an adrenolytic drug with delayed onset but long-lasting action. In general, medical treatment can also be considered for patients unwilling or unfit for surgery [53]. However, all these drugs have gastrointestinal side effects and hepatocellular dysfunction is frequently noted for ketoconazole with occasional cases of hepatic failure described [55, 56].

High doses of peroxisomal proliferator-activated receptor-γ agonist, rosiglitazone, have been shown to reduce ACTH and cortisol levels in animal models, but its effectiveness in human is not consistent [57]. Mifepristone is the first potent glucocorticoid receptor antagonist and has limited experience on patients with Cushing's disease. However, due to its long half-life, significant adrenal insufficiency may result [58].

Surgery

Cushing's Disease

Table 28.3 shows the immediate and long-term outcomes of surgery for Cushing's syndrome. Several series have shown the safety and favorable long-term outcome of transsphenoidal surgery for Cushing's disease [59–62]. Transsphenoidal surgery has the potential of achieving selective microadenectomy of the causative corticotrope adenoma and leaving the remaining pituitary function intact. However, the remission rate ranges from 42 to 86% (<15% for macroadenomas) [11, 63]. These variations in remission rates are attributed to the differences in surgical skills as well as controversy on the definition and characterization of

Table 28.3. Summary of surgical options and outcomes of surgical treatment for Cushing's syndrome

Etiology	Preferred surgical option	Outcomes	Factors affecting outcomes and long-term risk
ACTH-dependent			
Pituitary adenoma	Transsphenoidal surgery (TSS)	- Similar survival as normal population - 50–60% in remission	- Preoperative ACTH levels - ACTH response to CRH - Tumor size or invasiveness - Surgical experience - Risk of hypopituitarism
	Bilateral laparoscopic adrenalectomy (failed TSS)	- Low morbidity and mortality - Improved quality of life	- Risk of Addison's crisis - Nelson's syndrome (0–10%)
Ectopic ACTH syndrome	Resection of localized primary tumors	- Good immediate recovery	- Accuracy of localization - Presence of metastases - Nature of primary tumors
	Bilateral laparoscopic adrenalectomy (ACTH source not localized)	- Poor prognosis - Effective palliation	- Presence of metastases - Nature of occult ACTH source or primary tumor - Risk of Addison's crisis
ACTH-independent			
Adrenal adenoma	Laparoscopic adrenalectomy	- Excellent - Similar survival as age-match controls	
Adrenal carcinoma	Open radical adrenalectomy	- Poor	- Completeness of tumor resection
Adrenal hyperplasia	Bilateral laparoscopic adrenalectomy	- Excellent	- Risk of Addison's crisis

remission or persistent disease in the postoperative period. Larger, invasive, and more aggressive tumors are associated with worse outcome [59, 62] whereas centers performing a large number of pituitary operations have improved outcomes and minimal morbidity. If there is clear persistent disease postoperatively, immediate reoperation has been advocated [64, 65]. Despite a clinical and biochemical remission as evident by secondary adrenal insufficiency, there is still a recurrence rate of 5–25% during follow-up [63]. Glucocorticoids replacement is required for patients with secondary adrenal insufficiency postoperatively until the hypothalamo–pituitary–adrenal axis recovers full activity usually 6–18 months after surgery. There can be deficiencies of other pituitary hormones (hypopituitarism) in up to 50% over a long follow-up period.

For those with failed initial transsphenoidal surgery, bilateral laparoscopic adrenalectomy can be an alternative [66–68]. It is considered to be a potential primary treatment modality for selected individuals with Cushing's disease [66, 69]. This procedure is well tolerated with very little morbidity and a nearly 100% cure rate in patients with ACTH-dependent hypercortisolism. A recent study has found that those treated with bilateral adrenalectomy had equivalent quality of life as those cured by initial transsphenoidal surgery [68]. One major concern after bilateral adrenalectomy in patients with Cushing's disease is the development of Nelson's syndrome – a locally aggressive pituitary tumor that secretes high concentrations of ACTH (usually > 300 pg/ml) and results in skin pigmentation. For this reason, periodic MRI of the pituitary and measurement of basal ACTH are recommended after surgical treatment of Cushing's disease by bilateral adrenalectomy [7].

Ectopic ACTH-Producing Tumors

Resection of ectopic ACTH-producing tumors is undoubtedly the most effective way to reverse the hypercortisolemia and to cure the Cushing's syndrome. However, these tumors are not always amendable to complete or curative resection because of the frequent presence of metastases at presentation or the occult nature resulting in failure to locate the tumors. In these situations, either medical therapy or bilateral adrenalectomy should be employed. Bilateral adrenalectomy offers a rapid resolution of the hypercortisolism with minimal morbidity [69–71] and is increasingly being adopted.

Adrenal Causes

For unilateral cortisol-producing adrenal adenoma or carcinoma, unilateral adrenalectomy should be performed and laparoscopic approach has become the procedure of choice for benign adenomas [69, 72–75] (Fig. 28.5). Prognosis after removal of an adenoma is generally excellent [67, 76], but in contrast, if the tumor is malignant, the overall prognosis is poor. There remains controversy in adopting the laparoscopic approach for large, potentially malignant, or malignant adrenal mass. Open resection is generally recommended for frankly malignant adrenocortical carcinoma because of the potential increased risk of recurrence following laparoscopic approach [77, 78] For selected cases where conversion from laparoscopic adrenalectomy is required, the hand-assist technique may be utilized. In bilateral adrenal causes of Cushing's syndrome such as PPNAD and AIMAH, patients will benefit from bilateral laparoscopic adrenalectomy. The prognosis is generally excellent because both diseases are benign in nature [79].

Patients undergoing bilateral adrenalectomy will require life-long glucocorticoid as well as mineralocorticoid therapy and are at risk of having Addisonian crisis. Careful perioperative steroid replacement is essential and mineralocorticoid supplementation with fludrocortisone should be commenced at the same time when the patient is ready for oral intake. Stress-dose steroid supplementation (100 mg hydrocortisone intravenously every 8 h) should be administered in all patients and changed to oral form when diet has been resumed. The dosage can also be adjusted to a replacement dose (hydrocortisone or cortisone 20 mg a.m. and 10 mg p.m.) gradually after the operation. Even for unilateral adrenalectomy for adrenal adenoma or carcinoma, perioperative steroid cover should be administered and, in addition, steroid supplementation is required for 6–12 months after adrenalectomy for the hypothalamo–pituitary–adrenal axis of the contralateral suppressed adrenal gland to recover. In addition, patients with Cushing's syndrome are at increased risk of wound infection because of immunosuppression and should receive a single dose of perioperative antibiotic prophylaxis.

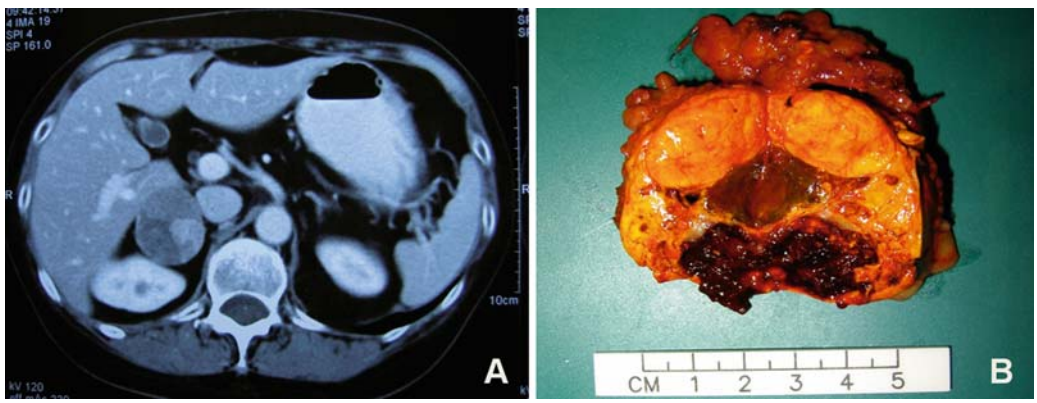

Fig. 28.5. CT scan showing a 3-cm adrenal adenoma in a patient with biochemically confirmed Cushing's syndrome (**A**) and the resected adrenal gland revealing a typical golden-yellow adrenal adenoma (**B**).

Conclusions

Cushing's syndrome is a well-recognized disease entity with heterogenous clinical presentation and underlying etiologies. The diagnosis of endogenous hypercortisolism is challenging and depends on a high index of clinical suspicion. Biochemical confirmation of the disease and hormonal evaluation of the underlying causes should be systematically performed followed by an accurate anatomical localization of the pathology. Treatment is primarily targeting at removing the causative pathology responsible for the hypercortisolism with an aim of long-term cure. Perioperative steroid cover is essential for patients with Cushing's syndrome undergoing surgical treatment. With surgical advances and improved perioperative care, patients with hypercortisolism can undergo surgical treatment with minimal risk and long-term cure.

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29

Pheochromocytoma and Paraganglioma

John R. Porterfield and Clive S. Grant

Pearls

- Pheochromocytomas account for 90% of chromaffin tumors
- Less than 10% of pheochromocytomas are malignant
- 24-h urine assay for metanephrines and catecholamines is 99% sensitive
- Computed tomography (CT) sharply defines the majority of tumors
- Magnetic resonance imaging (MRI) shows a characteristic "bright white" tumor on T2-weighted images
- Tumor excision is the only curative treatment
- Meticulous attention to detail at all stages of care is required for safety and success

Background

It has been over 120 years since a pheochromocytoma was first described at autopsy by Fränkel in 1886 [1]. Since this initial description, the care of patients with pheochromocytomas has challenged teams of physicians dedicated to unlocking the details surrounding these tumors. In 1926, Charles Mayo at Mayo Clinic and César Roux at University of Lausanne, Switzerland, excised the first pheochromocytomas, yet their diagnosis was unknown preoperatively [2, 3]. By 1951, 125 operations for pheochromocytomas had been reported with 33 perioperative deaths due to the ravages of extreme hypertension during resection or unrecoverable hypotension following tumor excision [4]. It was not until the advent of two pharmacologic agents: phentolamine for hypertension and noradrenalin for hypotension were these tumors able to be excised without drastic morbidity. Thus only 5 years later Dr. Priestley and colleagues reported the excision of 61 pheochromocytomas in 51 patients without a perioperative death [5].

Pheochromocytomas and paragangliomas are chromaffin tumors that arise from neural crest cells. The term pheochromocytoma refers to chromaffin tumors within the adrenal medulla and paragangliomas are thus chromaffin tumors that are found along the track of the embryological neural crest cells from the base of the skull, through the mediastinum, retroperitoneum, urinary bladder to the scrotum [6]. These tumors are capable of secreting large volumes of vasoactive amines. Pheochromocytomas have all of the necessary enzymes and cofactors to produce any or all of the catecholamines of the adrenal medulla. However, paragangliomas lack phenylethanolamine N-methyl transferase so they typically do not secrete epinephrine [7].

The incidence of pheochromocytomas is 2–8 cases per million persons annually [8, 9]. Since almost every patient presents with some degree of hypertension, this represents 0.1–0.2% of adult hypertensive patients [10]. Previously, 800

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deaths in the USA annually were attributed to complications from pheochromocytomas [11]. Of those whose diagnosis of pheochromocytoma was diagnosed on postmortem examination, three quarters of these deaths were secondary to a sudden severe myocardial infarction or cerebral vascular catastrophe. Tragically, one third of the sudden deaths occurred during or after unrelated minor operations [12].

Clinical Presentation

Pheochromocytomas typically occur in the fourth to fifth decade of life with a female predominance. The majority, 80–90% of pheochromocytomas, are thought to be sporadic in origin, with the remaining 10–20% being associated with genetic disorders [13]. Each year as thousands of researchers study the genetic associations of these tumors more genetic markers are identified. As a result many of those initially thought to be sporadic may be reclassified based on their genetic fingerprints in the years to come.

Pheochromocytomas have been termed the "ten percent" tumor since roughly 10% are malignant, bilateral, multifocal, extra-adrenal, inherited, incidentally discovered, and occur in children.

The typical presentation is that of a wide spectrum of symptoms due to catecholamine excess with the overwhelming unifying symptom at presentation being refractory or severe episodic hypertension. In addition most experience paroxysmal "spells" that are characterized by the classic triad of headaches, palpitations, and extreme hypertension. Following these spells, patients may remain hypertensive and thus many are treated for years for presumed "essential" hypertension. It may also be difficult to obtain accurate blood pressure measurements due to overwhelming peripheral vasoconstriction and Raynaud's type phenomenon. This profound increase in systemic vascular resistance combined with the direct adrenergic effects on the heart may lead to myocardial ischemia. This accounts for the increased incidence of sudden death in the patients identified to have pheochromocytomas at postmortem examination [12]. Half of patients are normotensive between episodes and some patients have periods of hypotension following spells [14]. The hypotension further reduces their diastolic coronary blood flow immediately following a bolus of epinephrine or norepinephrine thus exaggerating their risk of cardiovascular morbidity. The timing of the paroxysmal spells varies greatly from cycling as frequently as every 7–15 min to daily or weekly episodes [15]. These episodes may be initiated by nearly any mechanism that applies pressure to the tumor: increased intraabdominal pressure with defecation, urination (particularly with paragangliomas of the urinary bladder), child birth, vigorous physical exercise, sexual intercourse, or trauma. There are also chemical triggers to catecholamine release which may be stimulated by glucagon administration or alcohol ingestion. Importantly, patients may experience severe or even lethal complications related to paroxysmal spells brought about by invasive procedures such as diagnostic needle biopsy, angiography, general anesthesia, and unrelated surgical procedures [16]. Other symptoms that patients may experience include nausea, lassitude, heat intolerance, anxiety, abdominal pain, pallor, fever, or glucose intolerance.

Diagnosis

The diagnosis of a pheochromocytoma requires the identification of the classic signs as well as attention to clinical scenarios when hypertension is unexplained, refractory, or otherwise seemingly out of place. Examples of these scenarios include intermittent hypertension, especially labile hypertension, pregnant patients with new onset hypertension in the absence of preeclampsia, hypertension in children or in descendants of patients with pheochromocytomas, or genetic endocrinopathies [17]. With the increasing use of high-resolution imaging modalities more clinically silent adrenal lesions are identified. These patients should be screened for pheochromocytoma since the incidence of pheochromocytomas in a review of 42 incidentalomas at the University of California at San Francisco was as high as 33% [18]. Suspicious adrenal lesions should not be biopsied without confirmation of the absence of a pheochromocytoma to prevent a predictable severe complication [16].

Our initial study of choice to identify pheochromocytomas or paragangliomas is a 24-h

urine collection with evaluation of metanephrines and fractionated catecholamines, as analyzed by high-pressure liquid chromatography [19]. Despite the controversy regarding the measurement of urine versus plasma catecholamines, a 24-h urine collection has served our patients well with a combined sensitivity and specificity of 99% without the false-positive rate of 10% that accompanies plasma sampling [19]. When analyzing urine metanephrines and fractionated catecholamines, confounding substances or situations that may distort the results must be considered. The most frequent medications that interfere are the tricyclic antidepressants and thus these must be tapered and discontinued prior to testing [20, 21]. Labetalol, a combination alpha and beta antagonist also renders the 24-h urine testing less reliable. Methylglucamine is present in many iodated contrast dyes and may depress the metanephrine levels for up to 72 h. Other scenarios where 24-h urine studies may be unreliable include patients with advanced renal insufficiency, patients taking levodopa, or patients under extreme physiological stress (trauma, surgery, or obstructive sleep apnea) [21].

In patients with genetic predispositions to develop pheochromocytomas we do utilize plasma-free metanephrines as an initial screening tool, and it has an excellent sensitivity of 99% [22, 23]. Many laboratories also are able to measure serum levels of fractionated catecholamines (dopamine, epinephrine, and norepinephrine) and fractionated metanephrines (metanephrine and normetanephrine) by high-performance liquid chromatography with electrical detection or tandem mass spectroscopy. With these new analytical methods we are able to avoid many of the confounding substances as mentioned above and provide additional indications for plasma testing. Despite these advantages, the false-positive rate of 11–15% is troublesome for a general screening tool [19, 22, 23].

As a result of the advances in measuring catecholamines as discussed above provocative testing is rarely indicated. Of 542 patients at Mayo Clinic from 1975 to 1994 in whom there was a high index of suspicion of a catecholamine-producing tumor with normal 24-h urine studies not one tumor was found through histamine and glucagon stimulation testing [24].

To date no urine or serum study has been able to predict malignancy. The risk of malignant pheochromocytoma rises with increasing size as demonstrated by Shen et al. in their comparison of 90 malignant pheochromocytomas with an average size of 7.6 cm and 60 benign pheochromocytomas with an average size of 5.3 cm [25]. However, size alone also fails to predict malignancy reliably. Thus the diagnosis of malignancy in the absence of distant disease is determined intraoperatively by assessment of tumor invasion.

Localization

For a single localization technique to be perfect it would provide crisp anatomical detail, visual characteristics unique to the tumor, and allow the use of physiologic markers. There is no single "perfect" test for the localization of pheochromocytomas and paragangliomas, but fortunately we do have a triad of tests, when tailored to the clinical scenario, that provide the necessary information to counsel patients.

Greater than 90% of chromaffin tumors occur in the abdomen and pelvis. Therefore computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen and pelvis both localize these tumors and detect gross local invasion and solid organ metastasis [26]. Our initial imaging study is CT due to its prompt availability, relatively lower cost, and crisp anatomical detail. CT images of these tumors are heterogeneous due to their vascularity and central necrosis which is exaggerated with intravenous contrast (Fig. 29.1). The intravenous contrast carries some risk of triggering a hypertensive episode which may be avoided with pretreatment with an alpha antagonist [27].

MRI despite its higher cost and more lengthy examination does avoid radiation exposure and the use of venous contrast. T2-weighted images demonstrate a characteristic hyperintense, "bright white," signal that is characteristic for pheochromocytomas (Fig. 29.2) [28]. It may be contraindicated in patients with implanted devices that cannot tolerate a strong magnetic field or patients who are claustrophobic.

Iodine-131 or Iodine-123 tagged metaiodobenzylguanidine (MIBG) scan completes this triad of studies by producing a whole-body image to identify increased uptake of the physiologic marker that is specific to these

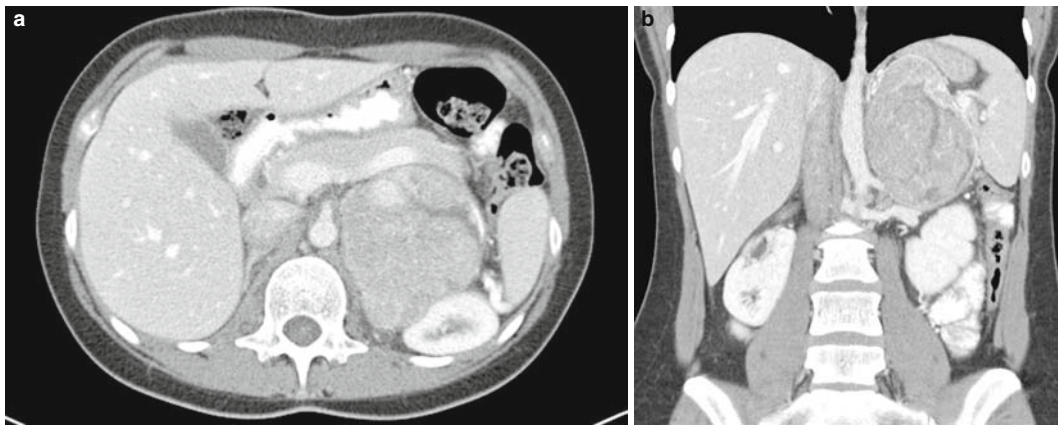

Fig. 29.1. (**A**) An axial CT scan, demonstrating a 10-cm left pheochromocytoma with areas of central necrosis displacing the pancreas and splenic vasculature anteriorly. (**B**) A coronal CT image of the same pheochromocytoma consuming the left upper quadrant.

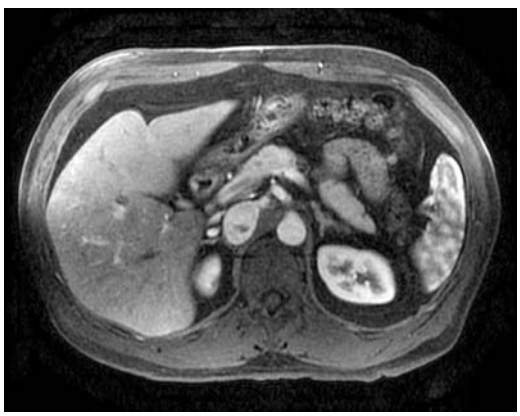

Fig. 29.2. MRI–T2-weighted image of retrocaval right-sided paraganglioma with central necrosis.

chromaffin tumors and their metastasis. It lacks anatomical detail and thus would not be used alone (Fig. 29.3). MIBG is the second test of choice when CT and/or MRI fail to localize a tumor that has been confirmed biochemically. The complexity of MIBG is significantly greater than CT or MRI in that it may require multiple scans over 48–72 h. MIBG also requires blockade of the thyroid with oral iodine for 1 day before and 3 days after scanning. This prevents the preferential accumulation of the radioactive iodine into the thyroid protecting it and providing for increased uptake by adrenal medullary tissue. In practice, MIBG is unnecessary in cases of sporadic pheochromocytomas identified by CT or MRI. Thus, its use is reserved for large pheochromocytomas (>10 cm) where malignancy is more likely and paragangliomas due to their increased incidence of multiplicity and malignancy in which it has a sensitivity of 91% [29].

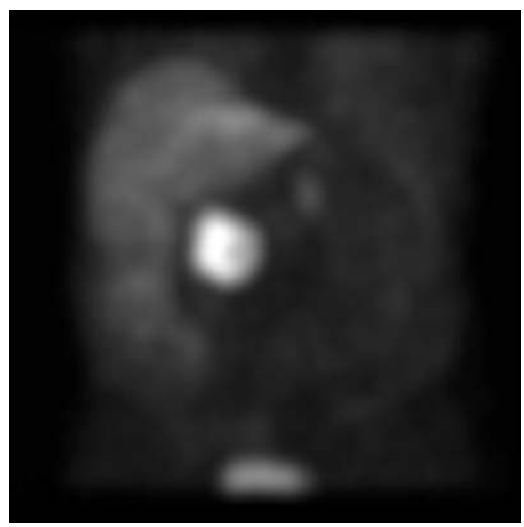

Fig. 29.3. A metaiodobenzylguanidine scan with SPECT imaging, demonstrating a right peri-aortic paraganglioma.

Preoperative Management

Surgical excision is the only cure for pheochromocytomas, and this requires experienced coordination between endocrinology, anesthesiology, and surgery. Dr. Priestley's sentinel publication demonstrated dramatic reduction in morbidity and mortality when patients were pharmacologically blocked thus blunting the hemodynamic responses associated with tumor manipulation and extirpation [5]. One should not be fooled by the apparent stability of patients who are normotensive with pheochromocytomas on initial evaluation as they may prove to be very unstable intraoperatively if not blocked preoperatively. Many institutions have their own unique protocols for preoperative blockade. We begin with alpha blockade followed by selective beta blockade and occasional use of inhibitors of catecholamine synthesis such as metyrosine.

Phenoxybenzamine (Dibenzyline®) is our alpha antagonist of choice which is administered for a minimum of 1 week. By its peripheral vasodilatation, it reverses the marked volume-contracted state driven by catecholamine-secreting tumor [30]. The starting dose is 10 mg orally once or twice daily increasing by 10–20 mg per dose as needed to treat their hypertension. Predictably, patients develop some degree of orthostatic hypotension and a "stuffy" nose which is a common distracting adverse effect [10]. Patients may require from 20 to 100 mg daily to achieve adequate blockade. During this period we counsel them to consume a high salt diet (5 g of dietary sodium) to aid with volume expansion. Only after adequate alpha blockade has been established should a beta adrenergic antagonist be considered. If this sequence is reversed the deleterious effects of a catecholamine surge accompanied with unopposed alpha stimulation may lead to a serious or even fatal hypertensive event. Calcium channel blockers and selective alpha-1 antagonist (prazosin/Minipress® and doxazosin/Cardura®) have been used with success at other institutions and carry the benefit of a shorter duration of action that may reduce the post excision hypotensive period. Calcium channel blockers cause peripheral vasodilation via vascular smooth muscle relaxation thus decreasing the peripheral vascular resistance. Unlike pure alpha antagonist they, by their cardiac effects, may also decrease the risk of catecholamine-induced coronary spasm [31].

Once the patient has been adequately blocked for a minimum of 1 week with an alpha adrenergic or a calcium channel blocker, beta adrenergic blockade may be required to normalize the heart rate, further lower blood pressure, and prevent cardiac arrhythmias. The dosage should begin low such as 10 mg of propranolol three times each day. This may be titrated as needed while paying particular attention to asthmatics and those with congestive heart failure as the beta blockade may result in acute pulmonary edema. While there are combination agents that block both alpha and beta receptors simultaneously we prefer the flexibility offered by the ability to titrate each to the needs of the patient.

In cases of refractory hypertension and/or tachycardia despite the above preparation it may be necessary to begin metyrosine (Dibenzyline®). Metyrosine is a competitive inhibitor of tyrosine hydroxylase, which prevents the conversion of l-tyrosine into l-dopa thus inhibiting catecholamine synthesis [32]. Metyrosine has a host of expected adverse effects which may be disabling and include sedation, diarrhea, anxiety, nightmares, and extrapyramidal signs [10].

Intraoperative Management

The operating theater must be properly prepared and suited for maximal hemodynamic monitoring and resuscitation. Prior to induction of a general anesthetic a radial arterial line may be indicated in labile patients despite blockade. At least two peripheral IVs should be placed and a Swan Ganz catheter may be used selectively in patients with severe cardiomyopathy. The current agents for treating hypotension (ephedrine 0.1–0.2 mg/kg and/or norepinephrine 4–16 μg/min) and hypertension (esmolol 12–200 μg/kg/min and/or sodium nitroprusside 2–4 μg/kg/min) should be prepared for immediate use [10]. We have found that the most volatile blood pressure swings occur with induction of anesthesia. As the procedure progresses with either a pneumoperitoneum or an open abdominal exploration the surgeon and the anesthesiologist must maintain excellent communication as each has significant hemodynamic

influence. With occlusion of the adrenal vein, the patient may rapidly vasodilate, requiring more vasopressor support and volume resuscitation. In our experience however many patients do not have this hemodynamic shift until the last seemingly insignificant venous attachments are divided.

Operative Techniques

There are several surgical approaches for resection of pheochromocytomas and paragangliomas. A unifying feature of any surgical resection of a pheochromocytoma or paraganglioma is that physical manipulation of the tumor should be minimized to reduce the hemodynamic swings that are present even in well-blocked patients. It is also essential that the capsule of the tumor not be violated as this may lead to an increased risk of local recurrence of otherwise benign lesions. Lastly, any minimal access procedure should be terminated in favor of an open exploration in cases of a difficult dissection, evidence of invasion, prohibitive adhesions, or surgeon inexperience.

Anterior Transperitoneal Laparoscopic Approach

During the last 15 years, we have experienced a dramatic change in the approach to adrenalectomy with the advent of transperitoneal laparoscopic adrenalectomy. As its safety has been demonstrated, its utility has been broadened from the first laparoscopic adrenalectomy for an aldosteronoma to the studies describing the utility of the laparoscopic approach for tumors up to 13 and even 15 cm [25]. The benefits of the laparoscopic approach have been well documented as in other abdominal procedures and they include shorter hospital stay, decreased blood loss, decreased pain, smaller incisions, and fewer complications [33].

The patients are positioned in a full lateral decubitus position with the side of the offending gland up. A pneumoperitoneum is established. On the right four trocars are placed along the right costal margin from the midline to the midaxillary line. A liver retractor (glass rod or "fan retractor") is placed through the medial most port which is crucial to provide exposure of the retroperitoneum. The triangular ligament is divided to allow further medial rotation of the liver and visualization of the peritoneum covering the right adrenal and inferior vena cava (IVC). The peritoneum adherent to the liver edge is incised with the cautery and the superior border of the adrenal gland is exposed. Similarly, the peritoneum adjacent to the lateral edge of the IVC is incised. The dissection then proceeds progressively superiorly along the right side of the IVC to expose the short adrenal vein which is isolated, clipped, and divided. The remaining attachments are then divided with electrocautery or a harmonic scalpel with careful attention to avoid violation of the capsule of the gland. Along the caudal most extent of the gland there are predictable arterial branches from the right renal artery and aorta which are typically best controlled with clips. The gland is then removed en bloc in a specimen bag and sent to pathology.

On the left side the trocars are placed similarly to the right; however, only three trocars may be necessary since the spleen does not require constant retraction when fully mobilized. Exposure of the left adrenal gland begins with mobilization of the splenic flexure of the colon and the division of the diaphragmatic attachments of the spleen with electrocautery. This allows for the development of a "trough" between Gerota's fascia of the kidney and the pancreas. As this exposure is further developed, the medial aspect of the adrenal gland is visualized and often the left phrenic vein may be traced to its junction with the left adrenal vein. The left adrenal vein arises from the left renal vein and is isolated, clipped, and divided. The phrenic vein may also be divided in a similar fashion. The gland is then mobilized with electrocautery or the harmonic scalpel. Similar to the right adrenal gland the left adrenal gland also has predictable inferiorly based arterial branches.

Anterior Open Approach

When patients have large tumors or a history of multiple upper abdominal operations an open anterior adrenalectomy may be elected. On both the right and left we prefer a long subcostal incision. A mechanical retractor is utilized to

elevate the costal margin superiorly. On the right the dissection proceeds very similarly to the description above for the laparoscopic approach. However, further mobilization of the liver is required, and sometimes also a partial Kocher maneuver to expose the IVC. The adrenal vein is then exposed and controlled. The exposure of the left adrenal gland may be obtained via either the medial mobilization of the spleen as described above or more typically via entrance into the lesser sac with cephalad retraction of the pancreas and spleen to expose the left adrenal gland and its vascular attachments.

Posterior Retroperitoneoscopic Approach

Although less common than the laparoscopic transperitoneal adrenalectomy, the posterior retroperitoneoscopic approach (PRA) is being performed in more centers worldwide each year. It provides the same benefits as the anterior laparoscopic approach in regard to small incisions, less pain, less blood loss, and early return to normal unrestricted activity. However, it extends a minimal access option to those who otherwise have hostile peritoneal cavities from previous upper abdominal surgery. Most surgeons have chosen the transperitoneal approach because of their familiarity with the anatomy. Walz and colleagues have reported on the largest series to date which included 560 adrenalectomies in 520 patients. The mortality was zero. The open conversion rate was 1.7% with a mean operative time of 67 min. Major complications occurred in 1.3% with minor complications in 14.4% [34]. Walz and colleagues have also reported their experience resecting 161 pheochromocytomas or paragangliomas via the retroperitoneoscopic approach in 126 patients. In 22 of 24 patients with bilateral disease cortical function was preserved [35]. In carefully selected patients this may prove to be a better option when compared to laparoscopic transperitoneal approach, but this has not been elucidated in the literature.

Patients are positioned in a prone position with the chest, pubis, and iliac crests supported by thick gel pads to allow the abdomen to "hang" thus allowing the kidneys to drop out of the operative field. The patients' hips are flexed to approximately 100° and the knees are bent 90°. The position of the bed is then oriented such that the lower back is parallel to the floor. A 1.5-cm incision is made at the tip of the twelfth rib. The fascia immediately inferior to the tip of the twelfth rib is entered bluntly and the subfascial pocket is developed with finger dissection. A 5-mm trocar is placed with bimanual direction 4–5 cm lateral to the initial incision, which is near the tip of the eleventh rib. Then a 10-mm trocar is placed 4–5 cm medial to the initial incision in a similar bimanual fashion. A 10-mm Hasson trocar is then placed in the initial incision and a capnoretroperitoneum is then established with a pressure between 20 and 28 mm Hg which does not cause hemodynamic embarrassment as would be expected with a pneumoperitoneum at these pressures. After a retroperitoneal space is created beneath the diaphragm with blunt dissection the upper pole of the kidney is identified and is depressed with an instrument. It is occasionally necessary to place a forth trocar to allow for the surgeon to have two available trocars for dissection. On both the right and the left the mobilization of the adrenal gland begins medially and caudally. On the right the vena cava is then exposed by division of the tiny arterial branches that cross the posterior surface of the vena cava. The right adrenal vein is then able to be visualized so that it may be clipped and divided. The gland is then detached from its remaining attachments with clips applied to arterial branches that cannot be controlled with cautery or the harmonic scalpel. On the left side the superior pole of the left kidney is identified after identical endoscopic retroperitoneal exposure. The dissection around the gland also begins medially and caudally allowing the gland to be lifted posteriorly exposing the left adrenal vein which is clipped and divided. The venous stump is also able to be used for retraction as the gland is lifted and its vascular attachments are divided. The gland with the associated tumor is removed en bloc via a silastic bag and sent to pathology [34–36].

Postoperative Management

The hemodynamic parameters of the patient are often very stable by the completion of the operation. Occasionally vasopressors and ongoing volume resuscitation will be required for a few

hours as the effects of the alpha blockade wear off in the absence of the catecholamine drive. It is reasonable for patients to be monitored in an intensive care unit for 24 h such that subtle changes in hemodynamics may be recognized promptly and treated. If a minimal access approach was utilized they may often be dismissed 48 h after tumor removal if their recovery has been uncomplicated. Two weeks postoperatively a 24-h urine collection for metanephrines and catecholamines is obtained to assure that all disease was removed and to serve as a baseline. We recommend annual 24-h urine collection for at least 5 years as metastatic disease may be latent 5 years or longer.

Mayo Clinic Rochester Experience

Between 1995 and 2006, 173 patients, 98 (57%) women and 75 (43%) men, underwent resection of pheochromocytomas. Their age ranged from 16 to 86 with a mean age of 54. Associated conditions were present in 23 (13%) including 8 multiple endocrine neoplasia (MEN) 2A, 5 MEN 2B, 6 VHL, and 4 with neurofibromatosis. Overall 59 (36%) of tumors were initially identified as incidentalomas. CT was the most common imaging modality utilized with no false positives, only 3 false-negative and 155 true-positive scans. MRI was utilized in approximately half with 1 false positive, 2 false negatives, and 70 true-positive studies. MIBG scanning was used selectively in 29 cases with 1 false-negative and 1 false-positive scan. The average size of tumors resected was 4.8 cm, range 0.7–16 cm. Preoperative blockade with phenoxybenzamine was used in 95% with the remaining blocked with calcium channel blockers such as nicardipine. Intraoperatively, despite preoperative pharmacologic preparation, 80% of patients required vasoactive medications to maintain appropriate hemodynamics. The average maximum systolic blood pressure was 192 with a maximum of 310, and the average minimum systolic blood pressure was 84 with a nadir of 31. The most common intraoperative agents used to control the patients' hemodynamic parameters have evolved to the short-acting agents esmolol and phenylephrine which were both used in just over 50% of cases. These were followed by labetalol and ephedrine which were used in approximately 30%, while sodium nitroprusside, which was commonly used in earlier years, was required in less than 10% of cases. Throughout this time, there has been a profound change from resecting the pheochromocytomas through an open anterior approach, to a laparoscopic method. In fact, in 2006, all of the pheochromocytomas were resected laparoscopically. Overall, 62% of these tumors were removed via the anterior transperitoneal laparoscopic approach, 33% were resected through an open anterior approach, and 5% were removed via an open posterior approach.

At Mayo Clinic, 48 abdominal paragangliomas were removed between 1992 and 2006. There was a slight female predominance of 56% compared to 44% in men. The average age was 13 years younger at 41 than the corresponding group with pheochromocytomas. Preoperative symptoms were present in 73% at initial presentation. Hypertension, present in 77%, was the most common presenting symptom. CT, MRI, and MIBG were found to have sensitivities for detecting abdominal paragangliomas of 95, 100, and 85%, respectively. We continue to prefer an open, anterior surgical approach for paragangliomas owing to the variability of the blood supply and difficulties often encountered in tumor mobilization.

Pathology

Pheochromocytomas and paragangliomas arise from the cells of the adrenal medulla or along the ganglia of the paramedian sympathetic plexus due to their derivation from embryological neural crests cells. Ninety percent of these tumors arise within the adrenal medulla. The most common location of paragangliomas is the organ of Zuckerkandl, at the aortic bifurcation [37]. These tumors are collectively classified as chromaffin tumors due to their origin and staining characteristics [38]. They appear as dark purple tumors due to their rich blood supply and may have cystic characteristics on their surface due to underlying tumor necrosis (Fig. 29.4). In the setting of previous adrenal hemorrhage one may find a dense inflammatory rind surrounding the tumor or atypical adhesions to surrounding organs from the resorbed blood products. They typically range from 2 to

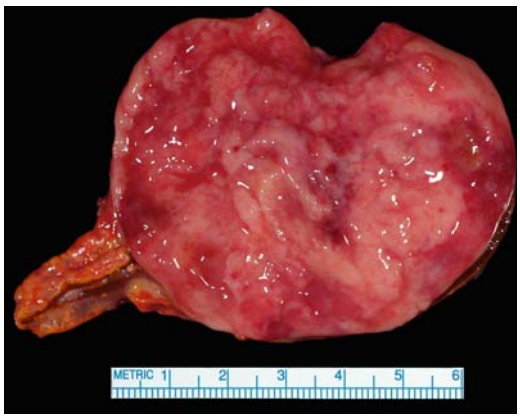

Fig. 29.4. Bivalved gross pathology photograph of 10 cm left adrenal pheochromocytoma demonstrating the soft grey "fish flesh" appearance of the tumor with normal cortex and medulla at the left of the image.

8 cm and weigh between 50 and 200 g. However both extremes are documented from the smallest at 50 mg and less than a centimeter in incidentally identified tumors to nearly 6 kg in a rare case of a 30-cm pheochromocytoma [39]. In sporadic cases the tumors are round or oval with occasional lobules despite the fact that they arise as a single neoplasm. In the absence of malignant transformation these tumors tend to have "pushing" rather than "invading" borders, and there is typically a plane separating surrounding structures visible on high-resolution cross-sectional imaging. In contrast, 40% of hereditary tumors are multiple either in the same gland or bilaterally [40, 41]. In MEN 2 there is a hyperplastic change of the adrenal medulla that is akin to the precursor C-cell hyperplasia preceding medullary thyroid cancer, but malignancy of pheochromocytomas in MEN 2 is rare [42].

Malignancy of either pheochromocytomas or paragangliomas is definitively diagnosed by recurrence, local invasion, or distant metastasis (Fig. 29.5). Discriminating benign from malignant on histologic evaluation has not generally been thought to be reliable. Kimura et al. have reported on a unique scoring system which assigns one or two points to the following criteria: (1) histologic pattern, (2) cellularity, (3) coagulation necrosis, (4) vascular or capsular invasion, (5) Ki-67 immunoreactivity, and (6) types of catecholamines produced. Specimens with 2 or fewer points were characterized as well differentiated (WD), those with 3–6 were moderately differentiated (MD) and those with 7–10 points were poorly differentiated (PD). Metastases were present in 13% of WD, 63% of MD, and 100% of PD tumors according to their tumor-scoring system. Thus using this scoring system metastatic potential and survival correlated well with 10-year survival of 83, 38, and 0% for WD, MD, and PD tumors, respectively [43].

Pheochromocytoma in Pregnancy

Hypertension during pregnancy may arise from a variety of causes but, in contrast to pheochromocytomas in pregnancy, few carry a mortality rate of 40% to the mother with up to a 56% fetal death rate [44]. The presentation during pregnancy is similar to that described earlier with the addition of supine hypertension as the gravid uterus compresses the tumor in the recumbent position. Thus, the typical lithotomy position during vaginal delivery would potentially provide maximal compression of the tumor. Additionally, the increased abdominal pressure during labor may lead to massive catecholamine release with life-threatening complications [45]. The overwhelming majority of patients with hypertension during pregnancy will not be due to pheochromocytomas but instead be attributed to preexisting secondary hypertension or preeclampsia. Preeclampsia is associated with sustained hypertension accompanied by proteinuria and is cured with delivery. Hypertensive pregnant patients should also be evaluated with serum electrolytes, glucose, creatinine, blood urea nitrogen, and urinalysis and culture to evaluate for secondary causes of hypertension such as renal disease, diabetes, and chronic pyelonephritis. When these studies are unrevealing and when hypertension is severe, positional or unexplained biochemical screening for a pheochromocytoma should be performed with a 24-h urine collection for fractionated metanephrines and catecholamines. Once the diagnosis is confirmed pregnant patients should be blocked. Blockade begins as described above with titration of an alpha blocker such as phenoxybenzamine followed by the addition of a beta blocker as indicated

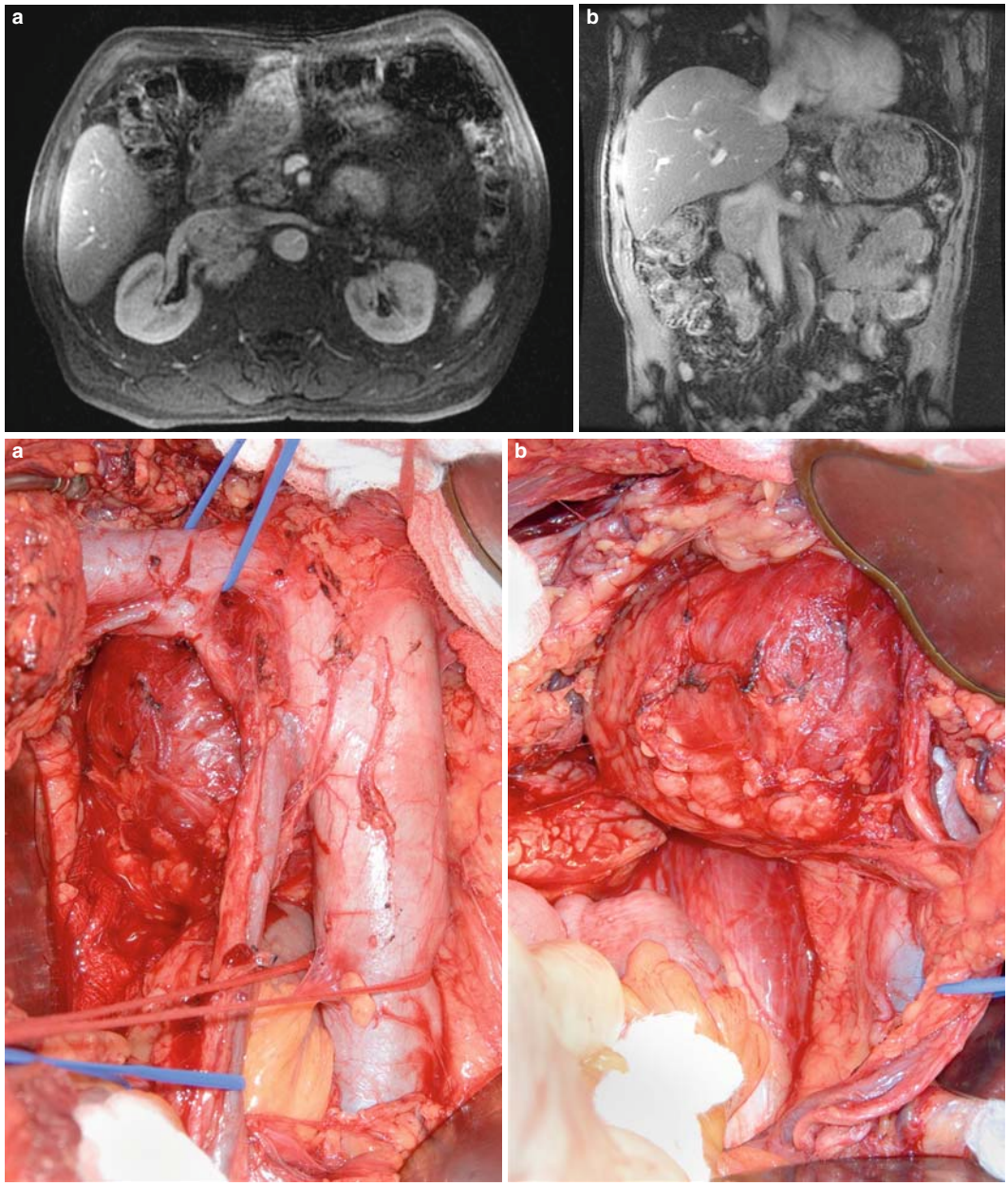

Fig. 29.5. (**A**) T2-weighted axial MRI of a paraganglioma displacing the right renal vascular pedicle anteriorly. (**B**) A T2-weighted coronal MRI of the same paraganglioma compressing the inferior vena cava. (**C**) Intraoperative photograph of the above imaged right paraganglioma which was displacing the right renal vein (RV) and inferior vena cava (IVC) anteriorly. (**D**) Intraoperative photograph with the right kidney mobilized anteriorly to expose the retrocaval right-sided paraganglioma.

for tachycardia [45]. MRI is the best imaging choice as it avoids the potential fetal risk of radiation with CT or I-123 MIBG.

The timing of surgery must account for the gestational age as with any abdominal procedure during pregnancy. These tumors are rarely identified during the first trimester as there is not sufficient uterine volume to compress the tumor. It is discouraged to perform any major abdominal procedure during this time as it is the

highest risk period for miscarriage with any major abdominal procedure. Although the second trimester is the "safest" period during which most urgent procedures are performed, blockade with meticulous follow-up from the twenty-fourth week on until a safe gestational age for delivery is advised. At the time of delivery a Cesarian section and combined tumor excision is recommended [45]. In one report following appropriate blockade an uneventful Cesarian section was followed 2 weeks later by a laparoscopic adrenalectomy [46].

Pheochromocytoma in Children

Pheochromocytomas cause 1% of hypertension in children [47]. During 40 years at a referral center for pheochromocytomas 58 patients were treated between the ages of 4 and 20 with 48% being associated with a known genetic syndrome [48]. The presentation in children is similar with the exception that the hypertension is more often sustained. The diagnosis is confirmed just as described in adults and imaging follows with CT, MRI, or MIBG scans. When localizing these tumors it must be considered that more tumors are bilateral and extra-adrenal due to the increased proportion of hereditary syndromes in children. However, it is encouraging that malignancy is identified less frequently than in the cases of hereditary chromaffin tumors in adults.

Genetic Syndromes

MEN Type 2 Syndrome

MEN type 2 (MEN 2) syndrome is linked in nearly all cases to mutations in the *ret* proto-oncogene and is characterized by medullary thyroid carcinoma, pheochromocytomas, primary hyperparathyroidism, and mucocutaneous neuromas [13]. In contrast to medullary thyroid carcinoma which is present in nearly 100% of those with this autosomal dominant syndrome, pheochromocytomas have a variable penetrance. In some kindreds 100% may be affected while other families may have less than 10% affected with pheochromocytomas. Overall 40% of those with MEN 2 will have a pheochromocytoma [49].

Once the biochemical diagnosis of a hypersecretory chromaffin tumor is identified in a patient with confirmed MEN 2 syndrome bilateral adrenal hyperplasia is certain [50]. This hyperplasia is a precursor to tumor development but the time course of this is variable [42]. There is a controversy regarding extent of adrenalectomy in these scenarios. In one series acute Addisonian crisis developed in 23% of patients following bilateral adrenalectomy [51]. In another report, at least 50% of patients did not require contralateral adrenalectomy within 5 years and no episodes of acute hypertensive crisis developed following unilateral adrenalectomy [52]. Therefore, it has become clear over time that initial bilateral adrenalectomy for patients with MEN 2 should be avoided due to the potential severe consequences. Our current practice is to perform a unilateral adrenalectomy with close follow-up, delaying the contralateral adrenalectomy until the patient is symptomatic and the tumor is visibile by cross-sectional imaging. This is due to the report of 33% of MEN 2 patients developing a contralateral pheochromocytoma within 5 years and only 52% within 12 years. Overall the average length of time to the development of a contralateral pheochromocytoma in MEN 2 following unilateral adrenalectomy is 13 years. Cortical sparring adrenalectomy has been increasingly performed for hereditary pheochromocytomas with the largest series of 59 patients reported from the MD Anderson experience between 1962 and 2003 [52].

Von Hippel Lindau Disease

Von Hippel Lindau disease (VHL) is an autosomal dominant syndrome characterized by a predisposition to tumors of the central nervous system, kidneys, pancreas, adrenal glands, and sympathetic ganglia. The occurrence of pheochromocytomas varies among kindreds between 7 and 20% [53, 54]. In our experience from 1975 to 2000, 109 patients with VHL were evaluated and 17 (16%) were found to have adrenal masses or paragangliomas. The ages ranged from 16 to 47 years with an average of 30 years. The majority, 60%, were asymptomatic

and 83% of tumors were identified by CT following biochemical evaluation. Only 2 of 17 underwent bilateral total adrenalectomy resulting in life-long corticosteroid replacement. There were no deaths or recurrences with a mean follow-up of 6.8 years (range 3 months to 37 years) [55].

Succinated Dehydrogenase Mutations (SDHB, SDHC, SDHD)

In 2002 Neumann and colleagues of the Freiberg–Warsaw–Columbus Pheochromocytoma Study Group reported on the genetic evaluations of 271 unrelated patients with nonsyndromic pheochromocytomas who had no family history of the disease [56]. They identified genetic mutations known to be associated with chromaffin tumors in 66 (24%). The mutations identified were 66% VHL, 35% SDH, and 20% RET. The mutations in the SDH (mitochondrial complex II) occur in the B, C, and D subunits. Patients with mutations in the C subunits are identified only in head and neck paragangliomas such as carotid body glomus tumors whereas the B and D subunits are additionally associated with paragangliomas and pheochromocytomas. The risk factors associated with the presence of one of these mutations was young age at presentation and the presence of multifocal or extra-adrenal tumors. Of the 23 SDH mutations 12 were SDHB and 11 were SDHD. None of these 23 had glomus tumors at presentation but 4 (17%) were found to have them identified during follow-up. Since nearly one quarter of these seemingly sporadic pheochromocytomas were identified to have germ-line mutations this has led us to pursue genetic testing in a stepwise fashion to better identify patients who need more specific screening and follow-up [56]. In general, the median age of initial diagnosis for SDH mutations is 30, and by age 40, the likelihood of an SDHB or SDHD mutation has been 45 and 75%, respectively. Tumors with SDHB mutations are likely to be extra-adrenal in 60%, malignant in 30–40%, and multiple in 10%. This compares to SDHD tumors of which 90% occur in the head and neck, 20% are extra-adrenal, 30% are multiple, and 10% are malignant. SDHD mutations carry maternal imprinting thus only paternal transmission leads to clinical effect. SDHC mutations are exclusively found in head and neck tumors and are rare, less than 4% of tumors. They are nonfunctioning, single, and benign in nearly every case.

Associated Conditions

In addition to the conditions described above pheochromocytomas also develop in association with the neuroectodermal disorders of von Recklinghausen's neurofibromatosis, Sturge–Weber syndrome, tuberous sclerosis, and Carney's syndrome. Carney's syndrome was described in 1977 by Dr. Aidan Carney and in his 1999 review of his experience combined with the world literature he reported on 79 patients with a combination of gastric epithelioid leiomyosarcoma, pulmonary chondroma, and paragangliomas. Among this group 10% had functional paragangliomas [57–59].

Summary

The classic triad of headaches, sweating, and hypertension should raise the suspicion of any clinician caring for a patient with what may be a life-threatening pheochromocytoma. With the increased use of high-resolution imaging these tumors are being identified more frequently before they are symptomatic and while they are small enough for laparoscopic or retroperitoneoscopic resection. The evaluation is based on the cornerstone of 24-h urine total metanephrines and catecholamines. However, the increased sensitivity of plasma fractionated metanephrines and catecholamines now provides for a more convenient screening tool as patients are followed for life. It remains almost impossible for the pathologist to differentiate the 90% of benign from the 10% which are malignant in the absence of local invasion or distant metastasis. As more genetic associations with these tumors are identified the routine follow-up will clearly be broadened for those carrying the mutations discussed above, and hopefully this will lead to earlier treatment of the conditions associated with these tumors to extend the lives of those affected. Modern preoperative blockade and careful anesthetic management currently provides intraoperative stability to allow for resection via laparoscopic or

retroperitoneoscopic routes. With the resection of these tumors the adrenergic symptoms are cured and the life-threatening complications of extreme catecholamine surges are meticulously prevented.

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30

Adrenocortical Carcinoma

Thierry Defechereux

Introduction

Adrenocortical carcinomas (ACC) remain, with anaplastic thyroid carcinoma, the most malignant endocrine tumors, and also, for physicians and surgeons trying to help patients, the most disappointing to treat.

The incidence of ACC is around 0.5–2 per million per year in adults [1], the estimated 5-year survival is between 19 and 30%, with a median survival time less than 12 months [2]. This hopefully rare tumor definitely has a bad prognosis.

The only hope of cure for ACC is diagnosis and surgery at an early stage; therefore, a main indication for adrenalectomy in patients with adrenal incidentaloma has been the potential risk of ACC.

Today up to 14% of adrenal incidentalomas are ACC. Yet despite the increasing use of more sensitive imaging studies that reveal potential ACC at an earlier stage, there has been no major change in the incidence of ACC, the extent of disease at presentation, or the number of ACCs treated surgically [2].

Although very recent data suggest a prolonged survival with Mitotane [3], adjuvant therapy is and remains questionable.

Molecular Pathogenesis

The molecular pathogenesis of ACC remains poorly understood. It is not clear whether a second hit paradigm is responsible for the transformation of an adrenal adenoma to an ACC [4–6]. Inactivating mutations at the 17p13 locus including the TP53 tumor-suppressor gene and alterations of the 11p15 locus leading to insulin-like growth factor (IGF-II) overexpression are frequently observed. Some in vitro studies suggest that overexpressed IGF-II acting via the IGF-I receptor is relevant for adrenal cancer cell proliferation [7, 8]. These being promising targets for future treatments in ACC.

Clinical and Hormonal Presentation

In most reported series, women are affected twice often as men [9–11], mean age is 42–47 years.

Patients present with evidence of adrenal steroid hormone excess in approximately 60% of cases. Rapidly progressing Cushing's syndrome with or without virilization is the most frequent presentation [12]. It seems that nonfunctioning ACCs are more frequent in men, and women <40 years more frequently have hyperfunctioning tumors [10].

Androgen-secreting ACCs in women induce hirsutism and virilization with deepening of the voice, male pattern baldness, and oligoamenorrhea. Estrogen-secreting adrenal tumors in males lead to gynecomastia and testicular atrophy and are almost invariably malignant [13]; virilizing tumors are malignant in 30% of cases.

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High concentration of dehydroepiandrosterone sulfate (DHEAS) is also suggestive of ACC, whereas a decreased level often signifies an adenoma. Aldosterone-producing ACCs present with hypertension and pronounced hypokalemia; however, severe hypokalemia commonly results from elevated cortisol secretion. Pure aldosterone-secreting tumors are malignant in less than 1% of cases [11].

It should be noted that the distinction between functional and nonfunctional ACC depends on the accuracy and completeness of the hormonal evaluation. A mild degree of endocrine overproduction – or production of steroid precursors – can be revealed in tumors lacking a clear-cut clinical syndrome. ACCs often have several defective steroid biosynthesis enzymes, causing elevated levels of steroid precursors [10]. An abnormal cortisol circadian rhythm and incomplete suppressibility by dexamethasone often occurs, regardless of the baseline steroid value.

Because steroid secretion in ACC displays a large variability, multiple sampling or combined determination of serum steroids and their urinary excretion, or both, are necessary to detect endocrine abnormalities. The low-dose dexamethasone test seems to possess a high-positive predictive value for the determination of an autonomous adrenal activity [14]. Adrenal steroid assays can be used as an equivalent of tumor markers for the early detection of tumor recurrence.

Arterial hypertension and metabolic alterations including increased fibrinogen, glucose, and lipids have been frequently associated at diagnosis and during recurrence, and should be monitored during follow-up.

According to Proye [11], patients presenting with an overt clinical syndrome of hypersecretion account for 60% of ACC cases while 30% present with a mass syndrome without clinical evidence of hypersecretion. The patients, in this latter group, complain of abdominal discomfort (nausea, vomiting, abdominal fullness) or back pain caused by a mass effect of the large tumor. Occasionally, patients present with fever, weight loss, anorexia, and asthenia; there may be signs of inferior vena cava compression. The remaining 10% of ACCs are found in adrenal "incidentalomas," and for these, there is no evidence in the literature that solid, nonsecreting adrenal lesions smaller than 3 cm in diameter are malignant.

The percentage of ACCs among incidentalomas removed represents 1.2% for the Mayo Clinic in 1999 [15] and 2% for Proye [11].

Staging

Determining whether an adrenal lesion is benign or malignant is not always easy. Clear-cut evidence of malignancy includes local surrounding invasion and metastasis, either synchronous or metachronous.

Major sites for metastasis are lung, liver, peritoneum, bone, the controlateral adrenal, and the brain. Local recurrence is not an absolute criterion of malignancy as disruption of a benign adenoma may result in seeding and recurrence.

ACCs are classified according to stages described by MacFarlane and modified by Sullivan [16]. The new UICC staging system published by the WHO in 2004 is based on this classification. Stages I and II describe localized tumors 5 cm or smaller and tumors larger than 5 cm, respectively. Locally invasive tumors with regional lymph node metastases are classified as stage III, whereas stage IV consists of tumors invading adjacent organs or presenting with distant metastases. This classification has one major drawback in that malignancy in stage I is based on histological criteria only. Whether all of these tumors are malignant may lead to an overly optimistic affirmation of the results of surgery [11]. Also some tumors less than 5 cm in size have spread into the peritoneal fat or into the kidney in the Association Francaise de Chirurgie Endocrine (AFCE) Study; they also decided that the loco regional invasion of cancer associated with invaded regional lymph nodes was not considered to represent stage IV disease, but were included in stage III as complete resection can theoretically be performed in such cases. Stage IV in this study had distant metastases [9].

Imaging

The size and the aspect of the adrenal mass on computerized tomography (CT), magnetic resonance imaging (MRI), and more recently 18 F-fluorodeoxyglucose positron emission tomography (FDG-PET) have been used to distinguish between benign and malignant lesions.

The size of the adrenal mass remains one of the best indicators of malignancy. Mean tumor size in different series ranges from 12 ± 6.0 cm [9] to 4–25 cm (med 11 cm) [10], 11.3±3.2 [1]. Mean weight 800 g.

ACCs smaller than 6 cm are frequently reported, and it is intuitively obvious that during early development ACCs are small and surgical intervention would be most beneficial at this stage. There is no doubt that tumors larger than 6 cm are highly suspicious and should be removed; no doubt that the likelihood of malignancy for tumors increase with size from 1.5 to 6 cm but remains limited because only 1 in 4,000 cases are malignant [11]. Operating on all patients with incidentalomas would probably result in more surgical deaths than patients cured by removing small ACCs.

Therefore, tumors between 3 and 6 cm represent the main challenge.

To avoid misclassification of small ACC as benign neoplasia, follow-up imaging is mandatory to detect early tumor growth and should be performed initially every 3–12 months depending on tumor size and radiological appearance. However, in young patients, life-long observation may not be cost-effective, and benign ACCs are less common in young patients. For patients with adrenal tumors larger than 6 cm, ACCs account for up to 15% of cases [17].

In addition to distant metastasis and tumor size, imaging studies can provide information suggestive of malignancy (see Fig. 30.1).

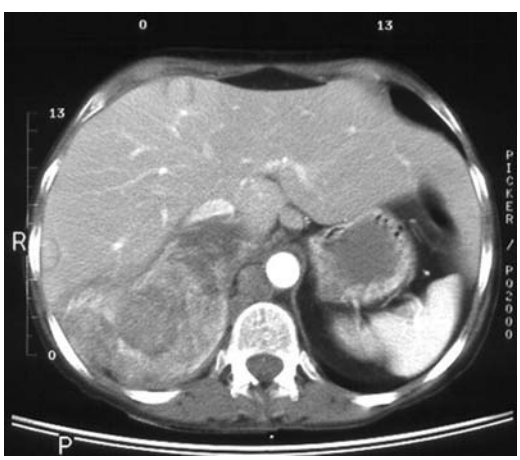


Fig. 30.1. Right adrenocortical carcinoma with two liver metastasis (stage IV).

On thin collimation CT, ACCs are inhomogeneous with irregular margins and irregular enhancement of solid components after IV injection of contrast. Sometimes calcifications are visible.

Local invasion or tumor extension into the inferior vena cava as well as lymph node or other metastases in lung or liver can be found. Measurement of Hounsfield units (HU) in unenhanced CT is of great value in differentiating a malignant from benign adrenal lesion. Using a threshold value of 10 HU, sensitivity and specificity for characterization of an adrenal lesion as a benign adenoma in enhanced CT was 71 and 98%, respectively, in a meta-analysis of 10 studies [18].

In other studies the median value for benign adenoma is around 19 and 36 HU for carcinoma [19]. For better discrimination of lipid-poor adenomas from ACC, a delayed contrast-enhanced CT can be used, analysing washout of contrast medium. Adrenal lesions with a attenuation value of more than 10 HU in unenhanced CT or an enhanced washout of less than 50% and a delayed attenuation of more than 35 HU (10 min) are suspicious of malignancy [20].

Modern MRI with dynamic gadolinium enhancement or assessing chemical shift are equally effective as CT in distinguishing malignant from benign lesions [21].

Once again the lipid content contributes to the differentiation between benign and malignant adrenal lesion; ACCs are typically isointense to liver on T1-weighted images and show intermediate to increased intensity at T2-weighted sequences. Enhancement after gadolinium is distinct and washout is usually slow. The sensitivity of MRI for differentiation of benign and malignant adrenal masses is 81–89% with specificity 92–99% [12, 21].

MRI is also useful in planning surgery because invasion into adjacent organs and inferior vena cava is best determined with this method.

Adrenal scintigraphy with noriodomethylcholesterol (NP-59) can be used and should demonstrate low uptake in ACC in the presence of normal controlateral uptake. The value of the exam is controversial and the diagnostic role is less than CT and MRI [11].

In contrast, recent studies have demonstrated good performance of PET-Scan in differentiating malignant from benign adrenal

lesions in patients with proven or suspected malignancy [22].

Adrenal Biopsy

In contrast to other tumor entities, *biopsy* of adrenal tumors has been controversial in the past and has never gained general acceptance because of needle tract metastases, tumor risk of spillage, and limited diagnostic value in differentiating benign from malignant lesions. Probable metastatic tumor to the adrenal is an exception in this matter, and for a very suspicious ACC, a biopsy can be performed (after excluding a pheochromocytoma) only if surgical excision is not feasible and the diagnosis cannot be established otherwise before starting medical adjuvant therapy.

Pathological Assessment

Pathological diagnosis should be performed by an experienced pathologist. Differentiation between benign and malignant adrenal lesions is based on the macroscopic features [tumor weight, hemorrhage, breached or intact tumor capsule, R-status (although not often available for the pathologist)] and the microscopic features using the Weiss score. This classification incorporates nine histological features, the presence of three or more of these features in a specimen correlates well with a clinically malignant outcome (nuclear atypia, atypical and frequent mitoses, vascular and capsular invasion, and necrosis). In addition, broad fibrous bands are a characteristic of malignancy separating ACC from adenoma.

The Weiss Histopathological system is now the most commonly used method for assessing malignancy because of its simplicity, reliability, and excellent interobserver agreement. Some of the criteria are, however, less reliable than others, and a modified system of weighting has been proposed by some authors with a significant correlation with the Weiss system [23. 11].

Major diagnostic problems arise in the evaluation of patients with tumors between 3 and 6 cm in diameter, exhibiting weak mitotic activity, with few areas of necrosis without obvious capsular invasion. In such cases, important additional information is gained from immunochemistry. Vimentin (14% positive for adenoma vs 80–90% for ACC [11]) and synaptophysin have been used to help distinguish between benign and malignant lesions; however, more recently, Ki67 [11], D11, inhibin-α, chromogranin A, and even more recently LOH, 17p13, IGF-II overexpression have been proposed to distinguish benign from malignant adrenal lesions. Ki67 expression may be of prognostic relevance as high expression ($\geq$10%) could be associated with poor survival (see Table 30.1).

Table 30.1. Weiss criteria for malignancy

High nuclear grade
Mitotic rate >5 per 50 high-power field
Atypical mitosis
Eosinophilic tumor cell cytoplasm (>75% of tumor cells)
Diffuse architectural pattern (>33% of tumor) with broad fibrous and trabecular bands
Foci of confluent necrosis
Venous invasion
Sinusoidal invasion
Capsular invasion

Treatment and Outcome

In most series, a particularly poor prognosis is reported for Stage IV ACC, with a median survival less than 12 months [12]; this of course is the most dramatic situation, but as a significant proportion (35–80%) of patients have occult distant metastasis at the time of initial presentation [24], the problem remains crucial overall.

Surgery

Only when an incidentally discovered ACC (10% of incidentalomas) or a stage I ACC is excised (R0), can surgery be considered as curative. Surgery offers the best chance for 'cure' in stages I–III when a specialized surgeon is the operator. R0 resection must be the goal, and extensive "en bloc" resection is often necessary with resection of invaded organs and large lymphadenectomy. Postoperative mortality for stages III–IV within 30 days of operation is about 10% [9].

Integrity of the capsule is mandatory in order to avoid tumor spillage and local recurrence.

The need to operate on patient with stage IV and distant metastasis is controversial due to the poor survival; although, tumor debulking may help to control hormone excess and may in individual cases facilitate other therapeutic options. Conversely, a young patient with a solitary metastasis should not be a contraindication.

Surgery for local recurrence or metastatic disease is accepted as a valuable therapeutic option and was associated with improved survival in some retrospective studies [25, 26].

A multivariate analysis identified the following independent prognostic factors associated with shorter survival: older age at diagnosis, initial Mac Farlane stages III and IV, and cortisol hypersecretion [1].

The poorer prognosis of Cortisol-secreting tumors may be related to comorbidity with Cushing's syndrome. It is also possible that the immunosuppressive effects of excess cortisol favor the development of the tumor and its metastases. Surgical morbidity can also be influenced.

Univariate analysis issued from the institute Cochin in Paris [1] showed that survival rates were higher for patients diagnosed since 1990; however, this effect was not observed in multivariate analysis adjusted for stage at diagnosis. This, of course, suggests that tumors now may be diagnosed at earlier stage than in the past (more stage II [12]). Incidentally detected ACC also had a better survival, and this might be related to the fact that they were diagnosed at an earlier stage and in more recent year reflecting improved and more widely available imaging technology.

Consistent with this hypothesis, a decreased percentage of patients with metastasis at diagnosis is detected in recent studies when compared with historical series (however only tumors under 5 cm were free of synchronous metastasis [9]). The French Surgical Study [9] also suggests that the higher rates of survival observed since 1998 are due to advances in perioperative care.

An extensive review of 725 cases of ACC treated between 1973 and 2000 from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) in the USA [2] demonstrated that there was no change in the incidence of ACC over the 28-year time period studied. Likewise there was no change in the extent of disease at presentation, or the number of ACC treated surgically. However, the cause-specific mortality decreased with time.

Laparoscopic surgery

The use of laparoscopic surgery for ACC is the subject of numerous debates. If laparoscopic adrenalectomy has become a gold standard for benign lesion with a diameter of less than 6 cm [27], for a larger tumor, the question remains [28], and, at present, there is a consensus that open adrenalectomy is the procedure of choice for proven ACC with (or even without) invasion of adjacent organs, enlarged regional lymph nodes, or tumor larger than 10–12 cm in size [29, 30].

Cobb et al. [31] reviewed the literature and identified 25 cases of ACC removed by laparoscopic resection. Local recurrence or intraperitoneal dissemination occurred in 40% of patients. High local recurrence after laparoscopic adrenalectomy was also observed in a recent series reported by Gonzales [32] and also previously by Hamoir [33].

Therefore laparoscopic adrenalectomy for ACC should be performed only in patients included in trials. Adrenal metastasis of lung cancer is however a good indication for laparoscopic removal, as is exploratory laparoscopy for a large adrenal mass without evidence of malignancy [28, 34].

The capsule of these white tumors can be thick or thin. When thin, with large superficial vein, the capsule is susceptible to rupture and local seeding; when thick, the capsule sticks to adjacent organs, the liver or the kidney, which may be invaded. Such adhesions may lead to extensive surgery; thus it is often wiser to search for a plane of cleavage under the liver or the kidney capsule. It is necessary to bear in mind that CT scans often overestimate local invasion.

Macroscopic venous invasion is common and more often observed on the right side, often encompassing the inferior vena cava. The neoplastic thrombus of an ACC can invade the venous wall, a vascular partial clamping for segmental removal can be necessary and even sometimes cardiopulmonary bypass when the thrombus invades the lumen of the vena cava.

A wide surgical exposure is mandatory for potential vascular control, tumor removal and

also removal of invaded adjacent organs. In the French study, 23% underwent a unilateral subcostal incision, 23% bilateral subcostal incisions, 22% thoracoabdominal incision, and 22% midline incisions [9]. In this series, surgery was curative (R0) in 71% of the cases, lymphadenectomy was performed in 33% of cases. En bloc resection beyond the adrenal was necessary in 42% of cases: kidney (29%), spleen (10%), VC thrombus (6%), liver resections (7%), and left pancreatectomy (4%).

Recurrence

Recurrences may occur long after initial treatment [1]; however, most recurrences and/or metastasis are diagnosed within 5 years of initial surgery. This observation may have important implications for patient information and follow-up; it may also provide a rationale for the duration of adjuvant therapy after curative surgery.

Unfortunately, the first recurrence is likely followed by other relapses, and the disease-free period is progressively shortened with upcoming recurrences being characterized by increasingly aggressive tumor behavior.

Adjuvant Therapy

Radiotherapy as an adjuvant treatment after surgery has been poorly studied, and although previously not recommended, a recent study demonstrated reduced local recurrence compared with matched controls [13].

Assessing the effectiveness of most published adjuvant treatment protocols for ACC has been difficult, since most series have been limited by the inclusion of relatively few subjects, with tumors at various stages.

Even in patients with apparently localized disease (stages I & II) and adequate surgery, metastases will very often develop within 6–24 months.

Mitotane

Mitotane (o,p′-DDD), is the only adrenal-specific agent available for the treatment of ACC. Mitotane exerts a specific cytotoxic effect on adrenocortical cells producing focal degeneration of the fascicular and particularly the reticular zone, whereas changes of the glomerulosa are relatively slight. Metabolic activation is essential for its adrenolytic activity.

Developing cancer cells will vary in their ability to metabolize Mitotane because of alterations in the metabolic process. Tumors with an ability to metabolize Mitotane respond, but those that are unable to metabolize the drug may not.

Mitotane treatment induces adrenal insufficiency and requires glucocorticoid replacement. Mitotane has a narrow therapeutic window. Several publications have established the impact of monitoring blood Mitotane concentration for predicting efficacy and toxicity (14 mg/l), as adverse effects occur frequently and are more often dose limiting. More than 80% of all patients experience at least one undesirable effect. Those are mainly gastrointestinal, or involve the central nervous system, leading in numerous cases to interruption of the treatment, also due to the lack of proven efficacy.

The dilemma facing the physician when there is no evidence of residual disease is whether to follow patients without initiating treatment or to use adjuvant therapy in the form of radiation, Mitotane, or systemic chemotherapy.

Numerous studies have shown that Mitotane fails to improve overall survival [9, 15], and that only 20–25% of patients respond in terms of tumor growth [12, 11]. Although the control of hormone excess exists in the majority of patients, a complete response in patients with advanced ACC is extremely rare, and survival advantage of Mitotane was apparently only proven in stage IV disease [9].

Given the toxic effects that are associated with what had been regarded as therapeutic doses and the lack of evidence for a real beneficial effect in previous studies, the use of Mitotane as adjuvant therapy for ACC has not been widely used.

Recently, a credible study from Terzolo et al. [3] came to the conclusion that patients receiving Mitotane after radical surgery had a recurrence-free survival that was two to three times as long as that of those not receiving the drug. Overall survival was increased in this group of patients. The study provides a compelling and very interesting rationale for the use of Mitotane as effective adjuvant therapy, even at low doses (1–3 g/day) (see Fig. 30.2).

Experience with cytotoxic chemotherapy in ACC is still limited, several combinations of agents have been used, and available evidence suggest that cisplatin alone or in combination

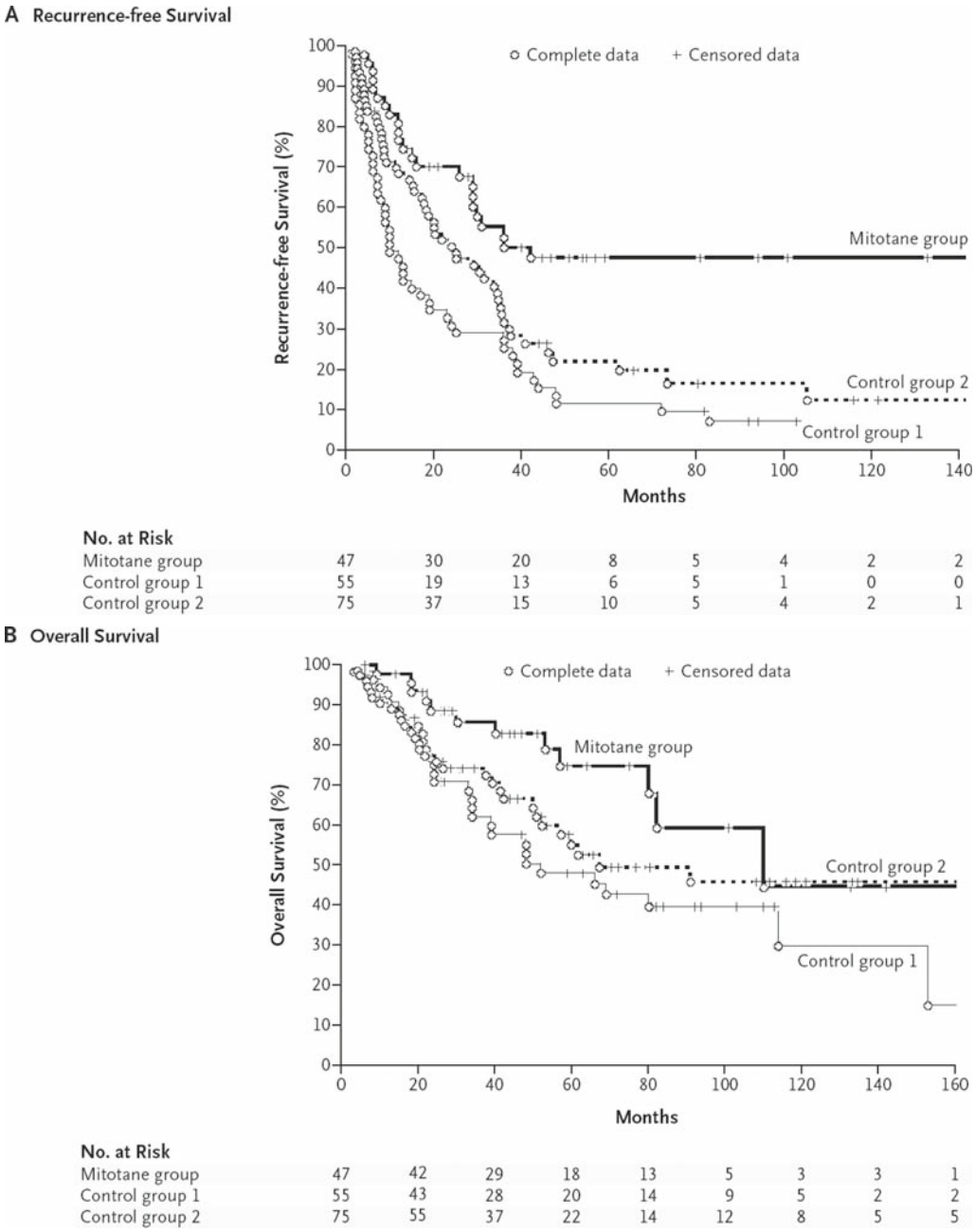
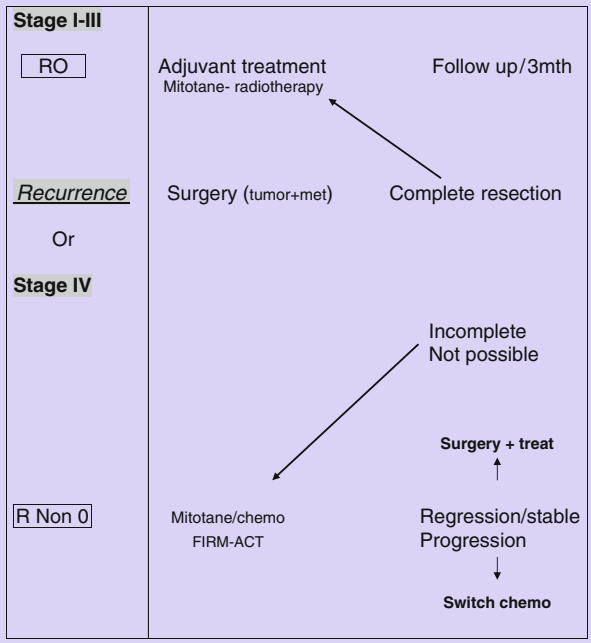


Fig. 30.2. Kaplan–Meier estimates of recurrence-free survival and overall survival. Reprinted with permission from Terzolo M, Angeli A, Fassnacht M et al. Adjuvant mitotane treatment for adrenocortical carcinoma. N Engl J Med 2007;356:2372–2380.

Table 30.2. Therapeutic strategy for ACC by stage and/or clinical situation



with etoposide has some activity in ACC. Only a minority of patients seem to respond to most of the protocols. An Italian protocol combine Mitotane, etoposide, doxorubicine, and cisplatin [35] with a response close to 50%, a less toxic protocol combining mitotane and streptozotocin has also been developed. A first phase III trial in ACC comparing those two regimens is currently ongoing (FIRM-ACT).

Hypersecretion of hormonal steroid can also be treated with other adrenostatic drugs such as ketoconazole or etomidate.

Future Prospects

After decades of limited progress, it seems that some progress in the treatment of ACC is taking place; however, current treatments remain disappointing and better therapies are needed.

Hope could come from therapeutic monoclonal antibodies, tyrosine kinase inhibitors, or immunotherapy, but true progress will only follow a better understanding of the molecular pathogenesis of ACC, and a better knowledge about tumor response to drugs that could greatly influence quality of life and prognosis of patients with ACC.

Conclusion

ACC is a rare neoplasm with a poor prognosis. Young patients present with signs of steroid hormone excess or an abdominal mass. Often, at initial diagnosis, metastases are already present, making the disease frustrating and disappointing to deal with for physicians and surgeons.

Complete tumor removal (R0 resection) offers the best chance for long-term survival, and therefore surgery is the treatment of choice in stages I–III ACC. Currently laparoscopic surgery is not recommended for proven ACC.

Despite tumor resection for cure, patients will very often develop local recurrence and distant metastases; thus adjuvant treatment options need to be considered. Nowadays, Mitotane is the best adjuvant treatment and according to recent data, is indicated for all patients (see Table 30.2).

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31

Incidentaloma

Dimitrios A. Linos

Introduction

Historically the adrenal tumor discovered incidentally, usually during an imaging procedure (CT, MRI, ultrasound) for symptoms unrelated to adrenal disease (e.g., back pain), is called an incidentaloma [1]. As more physicians order these easily available imaging studies for common diseases potentially related to adrenal pathology (and not the known syndromes), such as mild and nonparoxysmal hypertension, diffuse obesity, and diabetes, an increasing number of unsuspected (but hardly incidental) adrenal tumors are found. These tumors should be included with the true incidentalomas under the broader term "adrenaloma" because they share the same diagnostic and therapeutic dilemmas [2]. The term "adrenaloma" implies that the discovered tumor (incidentally or not) arises from the adrenal but is not obviously an aldosteronoma, a Cushing's syndrome adenoma, a pheochromocytoma, a virilizing or feminizing tumor, or a functioning adrenal carcinoma.

Recently at a State of the Science Conference at the National Institute of Health Conference, the term "Clinically Inapparent Adrenal Mass" was coined [3]. The widespread teaching is that most incidentalomas are indolent tumors, nonfunctioning, and asymptomatic, causing no harm to the patient [4, 5]. Recent studies, however, have shown that a high percentage of these tumors can be subclinically functioning, and cause symptoms milder than those encountered in the well-known adrenal hyperfunctioning syndromes but are still potentially harmful to the patient [6–14, 20, 33, 42, 46]. Thus, the suggested screening tests including serum potassium, urinary vanillylmandelic acid (VMA), and serum cortisol are not sufficient, and a more detailed and in-depth laboratory investigation is necessary. The fear of adrenal carcinoma that dictated the approach to these tumors in the past (with the main emphasis on the size of the tumor) should be changed to the fear of the subtle function of these usually benign adrenal cortical adenomas with coexistent metabolic pathology (e.g., hypertension, obesity, diabetes).

Frequency

The overall frequency of adrenal adenomas in 87,065 autopsies in 25 studies was 5.9% (range 1.1–32%) [15]. The frequency of adrenal masses discovered by CT, MRI, or ultrasonography is somewhat lower. Abecassis et al. [16] in a 2-year period examined 1,459 patients and found 63 (4.3%) with adrenal masses. Of those, 19 patients (1.3% of examined patients and 30% of patients with adrenal masses) had adrenalomas. At the Mayo Clinic [17], in a 5-year period with 61,054 patients undergoing CT scanning, an adrenal abnormality was found in 2,066 (3.4%) patients;

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among these, 259 patients (12.5%) had an adrenaloma or adrenal lesion larger than 1 cm, without biochemical evidence or symptoms suggestive of cortical or medullary hypersecretion or general constitutional symptoms suggestive of malignant disease. Similar findings have been described in more recent studies [18–20]. Thus, in the era of widespread use of high-resolution ultrasonography, new generation CT scans and MRI, a 5% incidence of adrenalomas is anticipated.

Pathology

The majority of surgically removed incidentalomas have been classified as nonfunctioning cortical adenomas [21–23]. Benign masses such as nodular hyperplasia, adrenal cysts, myelolipomas, ganglioneuromas, hematomas, hamartomas, hemangiomas, leiomyomas, neurofibromas, teratomas, as well as infections (tuberculosis, fungal, echinococcosis, nocardiosis) are also included in the pathology of these resected tumors. Potentially lethal neoplasms, however, such as pheochromocytomas and primary carcinomas are always first on the list of resected adrenalomas [24–28, 46]. Pheochromocytoma is the most frequently found hormone-producing adrenaloma that occasionally has a normal preoperative laboratory evaluation [29–34]. Few cases of aldosteronomas and androgen-producing adenomas have been described among cases of surgically removed adrenalomas [3–35]. In a large multicenter, retrospective Italian study of 380 surgically treated adrenalomas (out of 1,096 collected), 198 (52%) were cortical adenomas, 47 (12%) were cortical carcinomas, 42 (11%) were pheochromocytomas, and 93 (25%) were other less-frequent tumors [6]. Approximately 5% of incidentalomas are adrenocortical carcinomas.

The Goal of Evaluation

Although adrenal incidentalomas appear "non-functioning" by definition, more investigators have shown that a high percentage of them may be subclinically functioning and/or associated with other metabolic abnormalities based on clinical and essential laboratory findings (Fig. 31.1). In a multicenter, retrospective evaluation of 1,096 patients with adrenal incidentaloma, the work-up revealed that 9.2% had subclinical Cushing's syndrome, 4.2% had pheochromocytoma, and 1.6% had clinically unsuspected aldosteronomas [22].

Rossi et al. [10] prospectively followed 50 consecutive patients with incidentalomas. Detailed hormonal investigation found 12 of 50 (24%) to have subclinical Cushing's syndrome defined as an abnormal response to at least two standard tests of the hypothalamus–pituitary–adrenal axis function, in the absence of clinical signs of Cushing's syndrome. In the same study, 92% of patients had hypertension, 50% obesity, 42% type 2 diabetes mellitus, and 50% abnormal serum lipid concentrations. The clinical and hormonal features improved in all patients treated by adrenalectomy but were unchanged in those who did not undergo surgery (follow-up 9–73 months).

Interestingly, all 13 patients who had resection of truly nonfunctioning adenomas because of large size had improved clinically to such an extent that antihypertensive and antidiabetic therapy was reduced or discontinued. All the improvements persisted during follow-up.

Another multicenter study [12] of 64 consecutive patients with adrenal incidentalomas found a higher than expected prevalence of abnormal glucose tolerance in 39 (61%) patients. The same authors [36] following 62 consecutive patients with adrenal incidentalomas found abnormal glucose tolerance curves in 66%.

Midorikawa et al. [11] studying 15 patients with incidentalomas (4 with subclinical Cushing and 11 with truly nonfunctioning tumors) found a high prevalence of altered glucose tolerance and insulin resistance. Adrenalectomy reversed insulin resistance in all patients with subclinical functioning and truly nonfunctioning adrenal adenomas.

Terzolo et al. [8] followed 41 patients with incidentalomas (12 with subclinical Cushing's syndrome) and compared them with 41 controls. He found that the 2-h post-challenge glucose was significantly higher in these patients than in controls. Similarly, both systolic and diastolic blood pressures were higher in studied patients. The calculated whole-body insulin sensitivity index (derived from the oral glucose tolerance test) was significantly reduced in the patients. They concluded that patients with these tumors (subclinically functioning or

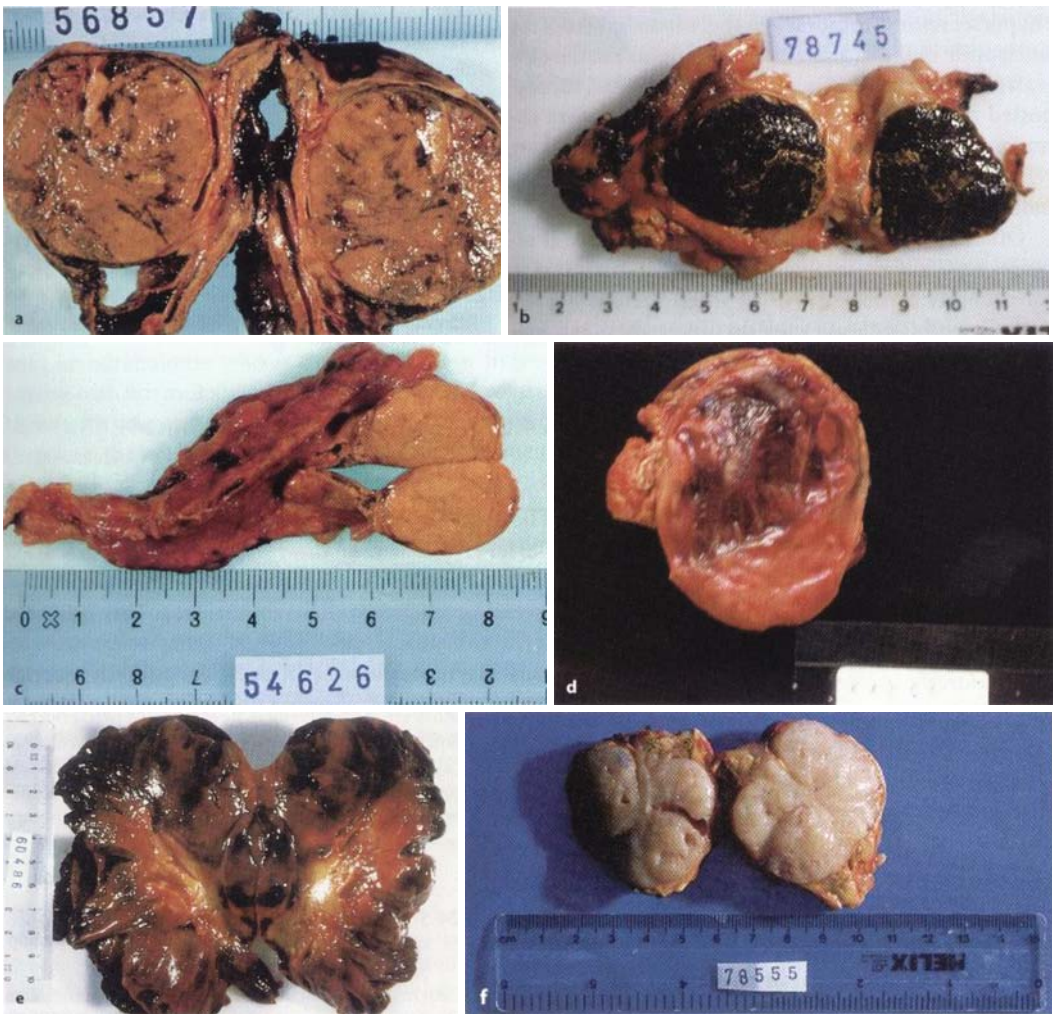

Fig. 31.1. Adrenal incidentalomas with "unexpected" clinical behavior. (**a**) Cortical adenoma on a 37-year-old female with subclinical Cushing's syndrome and metabolic syndrome significantly improved after surgery. (**b**) Cortical adenoma on a 40-year-old male that during a 3-year follow-up turned from "nonfunctioning" to overt Cushing's syndrome. (**c**) Aldosteronoma on a 45-year-old hypertensive but normokalemic male followed for years for this 2.5 cm "incidental" mass. (**d**) Pheochromocytoma on a 32-year-old asymptomatic normotensive female. (**e**) "Indolent" myelolipoma that ruptured during its follow up causing severe intra-abdominal bleeding on a 27-year-old male. (**f**)Solitary metastatic adrenal carcinoma, 10 years after hysterectomy for cervical cancer on a 62-year-old female. (Reprinted with permission from Linos DA, Adrenal glands: diagnostic aspects and surgical therapy. Heidelberg: Springer-Verlag; 2005. 243).

nonfunctioning) display some features of the metabolic syndrome such as impaired glucose tolerance, increased blood pressure, and high triglyceride levels.

Garrapa et al. [13] evaluated body composition and fat distribution, as measured by dual-energy X-ray absorptiometry (DEXA) in women with nonfunctioning adrenal incidentalomas and in women with Cushing's syndrome compared with healthy controls matched for age, menopausal status, and body mass index (BMI). Women with adrenal incidentalomas had larger waist circumference reflecting intraabdominal fat. The blood pressure was higher in patients with these tumors than in controls, and 50% of patients were hypertensive.

High-density lipoprotein cholesterol levels and mean triglyceride values were also higher in patients with adrenal incidentalomas than in controls. If central fat deposition, hypertension, and low HDL are important risk factors for cardiovascular disease, then patients with adrenal incidentalomas, whether subclinically functioning or nonfunctioning, are at higher risk than the general population for cardiovascular disease.

Chiodin et al. [14] performed a longitudinal study evaluating the rate of spinal and femoral bone loss levels in 24 women with adrenal incidentalomas. They were divided into two groups on the basis of the median value of urinary cortisol excretion. The group with higher cortisol values (subclinical Cushing levels) had more lumbar trabecular bone loss than those with low cortisol secretion (not hypersecreting tumors).

Therefore the cavalier attitude toward adrenal incidentalomas should be changed. These tumors are in between the normal and the pathological stage. They should be screened to rule out (1) subclinical Cushing's syndrome, (2) subclinical pheochromocytoma, (3) subclinical primary aldosteronism, and (4) adrenal carcinoma (primary or solitary metastasis).

Screening for Subclinical Cushing's Syndrome

Patients with subclinical Cushing's syndrome have none of the signs and symptoms of typical Cushing's syndrome (plethora, moon face, central obesity, easy bruising, proximal muscle weakness, acne, osteoporosis, etc.). The frequency of subclinical Cushing's syndrome among patients with adrenaloma ranges from 12 to 24% [10, 37]. Depending on the amount of glucocorticoids secreted, the clinical significance of subclinical Cushing's syndrome ranges from slightly attenuated diurnal cortisol rhythm to atrophy of the contralateral adrenal gland, a dangerous condition after unilateral adrenalectomy if appropriate perioperative therapeutic measures are not taken early enough [38].

The best screening test for autonomous cortisol secretion is the short dexamethasone suppression test. A suppressed serum cortisol (<2 μg/dl or 50 nmol/l) excludes Cushing's syndrome. A serum cortisol greater than 2 μg/dl requires further investigation, including a confirmatory high-dose dexamethasone suppression test (8 mg), a corticotropin-releasing hormone (CRH) test, analysis of diurnal cortisol rhythm and growth hormone (GH) response to GHRH [8]. If serum cortisol concentrations are not suppressible by high-dose dexamethasone, the diagnosis of subclinical Cushing's syndrome is established. As already discussed, glucose tolerance is altered in patients with adrenal incidentalomas (with and without subclinical Cushing), and a glucose tolerance test is recommended in patients with adrenal incidentalomas [10, 12, 39]. Finally, bone mineral density of the spine should be performed to detect reduced bone mass in patients with subclinical Cushing's syndrome [14].

Adrenal scintigraphy with ^{131}I-6β-iodomethylnorcholesterol (NP 59) can reveal a "functioning" but not "hypersecretory" tumor when there is an uptake of the nucleotide in the tumor site and no-uptake in the contralateral suppressed gland. Some authors [40, 41] showed a significant positive correlation between abnormal cortical secretion and NP 59 uptake, while others [15] considered NP 59 scanning not cost-effective because it requires several days to obtain the images. In addition, routine use of NP-59 scan is not recommended because of the inability of adrenal gland with hemorrhage or inflammation to take up NP-59.

Screening for "Subclinical Pheochromocytoma"

The typical patient with pheochromocytoma is hypertensive and may have paroxysmal hypertension and related symptoms (headache, hypertensive crisis, sweating, and cardiac arrhythmias). The proposed term "subclinical pheochromocytoma" refers to the totally asymptomatic adrenal incidentaloma that histologically proves to be a pheochromocytoma. In several series of adrenal incidentalomas, the frequency of pheochromocytomas ranges from 10 to 40% [31, 34]. Although the percentage of asymptomatic pheochromocytomas among patients with nonfunctioning adrenal tumors is relatively high, hormonal evaluation, which is a measurement of 24-h urinary metanephrines and VMA or fractionated urinary catecholamines, is commonly diagnostic. In the National Italian Study Group, 27 patients (3.4% of

the total patients with incidentaloma) were found to have pheochromocytoma; 24-h urinary catecholamine and VMA concentrations were elevated in 86 and 4.6% of patients, respectively [22], indicating that a combination of tests is more useful clinically than an individual test. The efficacy of single-voided ("spot") urine metanephrine and normetanephrine assays for diagnosing pheochromocytoma has recently been documented. Such tests may avoid the inconvenience of 24-h urinary collection [42].

Ten of 42 patients (24%) with adrenal incidentaloma had borderline evaluations in urine or plasma metanephrine levels, three of whom had a pheochromocytoma (30%) in a recent study [42]. Interestingly, in these 10 patients no clinical factors such as hypertension, symptomatology, or size allowed differentiation between those with and without pheochromocytomas. Preoperatively, it is wise to prepare this group of patients (with incidentaloma and borderline metanephrine levels) with alpha blockade knowing that only a percentage of them will eventually have histologically proven pheochromocytoma. On the other hand, there is no indication for routine use of ^{131}I-meta-iodobenzylguanidine (I-MIBG) scintigraphy in the evaluation of an adrenaloma unless catecholamine and urinary metabolites are elevated.

Screening for "Subclinical Primary Aldosteronism"

Typical primary aldosteronism is characterized by hypertension with hypokalemia, elevation of plasma aldosterone, and suppressed plasma renin activity (PRA). Subclinical primary aldosteronism describes the patient with adrenaloma who is normotensive or hypertensive with normokalemia [43]. More than 40% of patients with primary aldosteronism are normokalemic; therefore, the previously recommended measurement of potassium as the only test to rule out primary aldosteronism in the case of adrenal incidentalomas should be abandoned [43]. Instead, a detailed time-consuming evaluation is necessary, especially in all hypertensive patients, to rule out primary aldosteronism, which may be the cause of hypertension in up to 15% of these patients [44, 45]. In a normotensive patient with a serum potassium level greater than 3.9 nmol/l, no further hormonal evaluation is necessary. The screening for subclinical primary aldosteronism should include, in addition to serum potassium, the upright aldosterone level to PRA ratio, since a single value of aldosterone may be normal. Patients with two or more samples of positive aldosterone/PRA ratio (>40) should undergo the fluorocortisone suppression test (0.4 mg every day for 4 days) or the acute saline-suppression test (2 l of 0.9% NaCl solution infused intravenously in 4 h) to confirm the diagnosis. Bilateral adrenal venous sampling with measurements of aldosterone and cortisol levels is the necessary next step to lateralize and to determine the subtype of primary aldosteronsim in order to identify the patient who will be cured through surgical treatment.

Screening for Adrenal Carcinoma

The risk of an adrenal incidentaloma harboring a primary carcinoma of the adrenal varies from 4 to 25% depending on the size of the tumor [46, 58]. The annual incidence of the latter has been estimated to range from 1 case per 600,000 to 1 case per 1.6 million persons. Its prevalence is approximately 0.0012% [47]. In contrast, metastatic carcinoma to the adrenal is a common finding in patients with lung, breast, colon, and other extra-adrenal malignancies. In published series of surgically resected adrenalomas, the frequency of histologically confirmed primary adrenal carcinoma ranges from 4.2 to 25% [6]. The frequency of adrenal metastasis from lung cancer at autopsy ranges from 17 to 38%. In patients with an adrenal mass in the setting of extra-adrenal malignancy, the probability of this mass being metastatic ranges from 32 to 73% [5, 34, 48].

Size of Tumor

The size of an adrenal incidentaloma is frequently used to predict potential malignancy and the need for surgery. Although most clinically treated adrenal malignancies are discovered when they are larger than 6 cm in diameter, several reports have described very large tumors that never metastasized and small

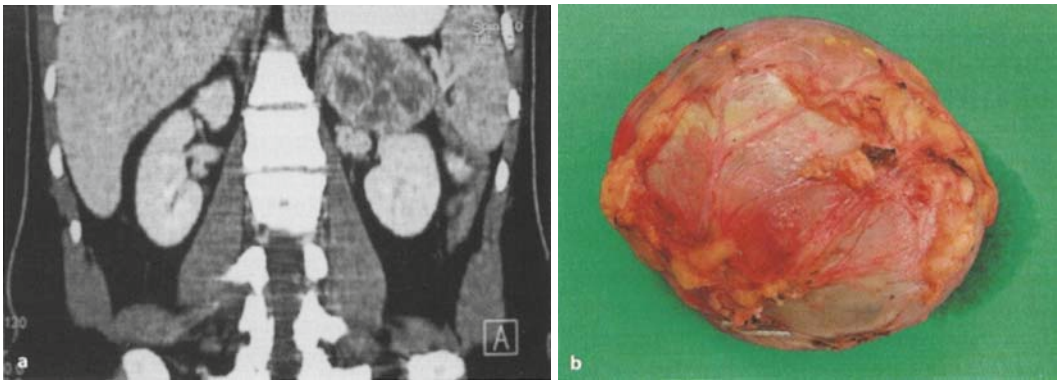

Fig. 31.2. This larger than 6-cm adrenal incidentaloma was suspicious for malignancy on CT scan (**a**) but histologically was proved a benign cortical tumor (**b**). (Reprinted with permission from Linos DA, Adrenal glands: diagnostic aspects and surgical therapy. Heidelberg: Springer-Verlag; 2005. 246).

adrenal tumors that did (Figs. 31.2 and 31.3). In several series, adrenocortical carcinomas with a maximum diameter of 3 cm or less have been described [15, 34, 38, 48].

The size of an adrenal incidentaloma as reported on a CT scan is usually less than the size reported on the histology report. This underestimation ranges from 16% to 47% [49]. In an analysis of the CT and histology reports of 76 patients with various diseases, we found that the mean estimated diameter of the adrenal tumor was 4.64 cm on the CT report when the real size (pathology report) was 5.96 cm. Further analysis of different CT scans revealed a consistent underestimation in all groups. In the group of adrenal tumors with a maximum diameter of less than 3 cm, the mean diameter reported on CT was 2.32 cm in contrast to the true histological size of 3.63 cm ($p < 0.001$). We therefore proposed the formula Histologic Size $= 0.85 + (1.09 \times$ CT size) to correct the underestimated CT size so as to use the size criterion more accurately [49]. A study from Mexico [50] showed that the above "Linos formula" turned out to be significantly more accurate than the direct radiologic measurements in predicting the real pathological size of the tumor.

Imaging

In addition to assessing distant metastasis and tumor size, imaging studies may suggest malignancy. On CT, one may see a poorly delineated ragged tumor with stippled calcifications and with areas of necrosis; such lesions are suggestive of malignancy, especially if enlarged lymph nodes or local invasion is also detected.

On MR imaging studies, one should look for heterogeneously increased, early T2-weighted signal, weak and late enhancement after gadolinium injection or an intravascular signal identical to the tumor signal. When NP59 scintigraphy is available, the lack of (or very weak) uptake in the tumor and normal contralateral uptake is suspicious for malignancy. Positron emission tomography (PET) can be used following the administration of 2-deoxy-2[^{18F}] fluoro-D-glucose. The 18F-FDG-PET scan is a useful tool confirming isolated metastases and in selecting patients for adrenalectomy. It has been used in studies to distinguish between primary and metastatic adrenal lesions, especially in patients with other primary malignancies [51] (Fig. 31.4). In patients with oncologic history the combination of MRI and 18F-FDG-PET scan provided accurate differentiation between metastases and benign adenomas as illustrated in one study of 42 patients with adrenal incidentalomas [52].

Fine-Needle Aspiration

Fine-needle aspiration (FNA) biopsy of an adrenal incidentaloma has a limited role. It is useful in cases of coexistent extra-adrenal malignancy (usually lung cancer) to confirm the radiologic evidence of adrenal metastasis. Generally, FNA cannot differentiate cortical adenoma from carcinoma because it cannot detect invasion of the

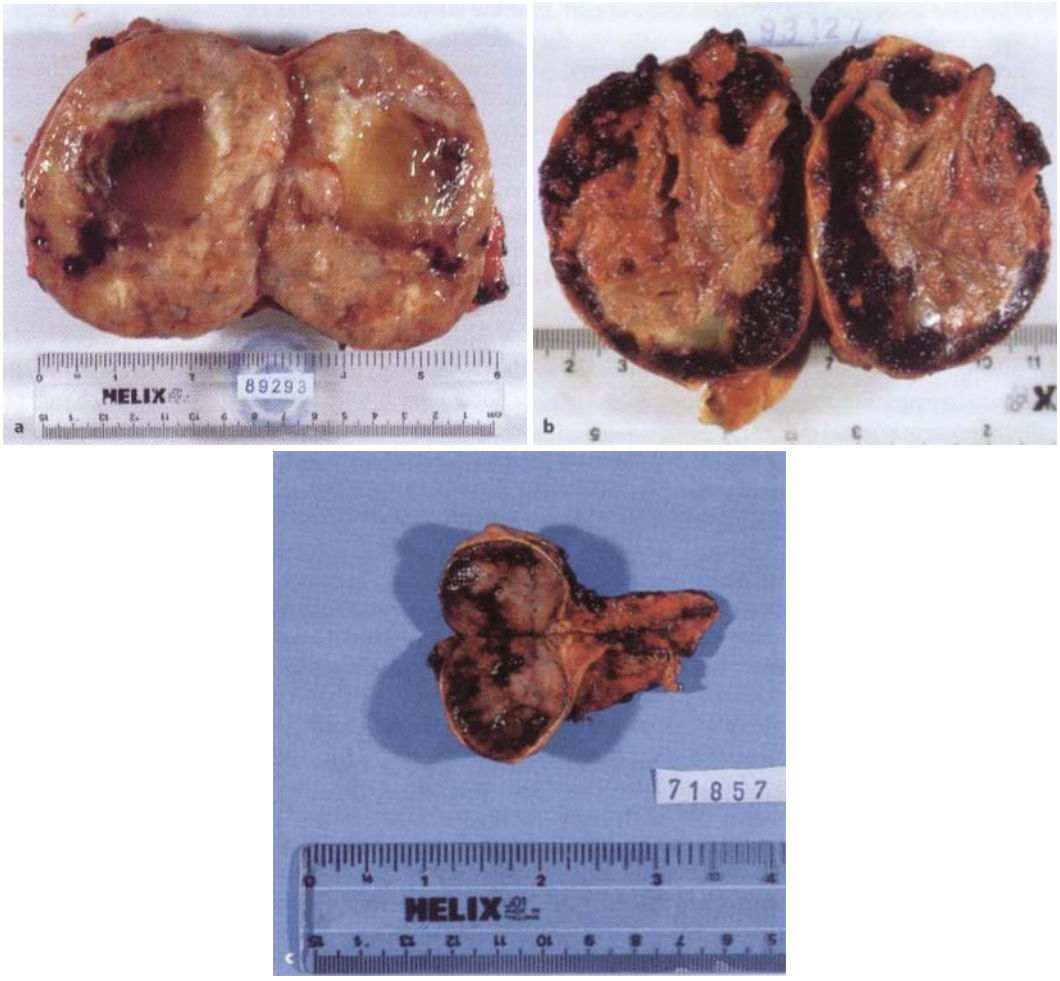

Fig. 31.3. The size of the adrenal incidentaloma does not necessarily predict the clinical severity of the problem. (**a**) A 9-cm maximum diameter benign schwanoma. (**b**) A 7-cm maximum diameter benign hemorrhagic cortical adenoma. (**c**) A 2.9-cm potentially lethal pheochromocytoma. (Reprinted with permission from Linos DA, Adrenal glands: diagnostic aspects and surgical therapy. Heidelberg: Springer-Verlag; 2005. 247).

tumor into the capsule. In a study by Silverman and coworkers [53], 3 of 33 FNA specimens that contained "benign" adrenal tissue were later proved to be malignant. Each malignant lesion was smaller than 3 cm in diameter. In 14 patients in whom the FNA was nondiagnostic, two masses proved to be malignant. Although it has been suggested that FNA is useful in the differential diagnosis of a cystic adrenal mass, such practice is not recommended because cystic pheochromocytomas are prevalent. Diagnostic puncture of such a lesion (or of a rare cystic echinococcal parasitic cyst) can be harmful to the patient. The possibility of seeding a malignant adrenal neoplasm in the retroperitoneum is an additional reason that FNA should be discouraged.

Genetic and Molecular Biology Studies

Currently, the only accepted confirmatory criteria to determine whether an adrenal incidentaloma is benign or malignant are the presence

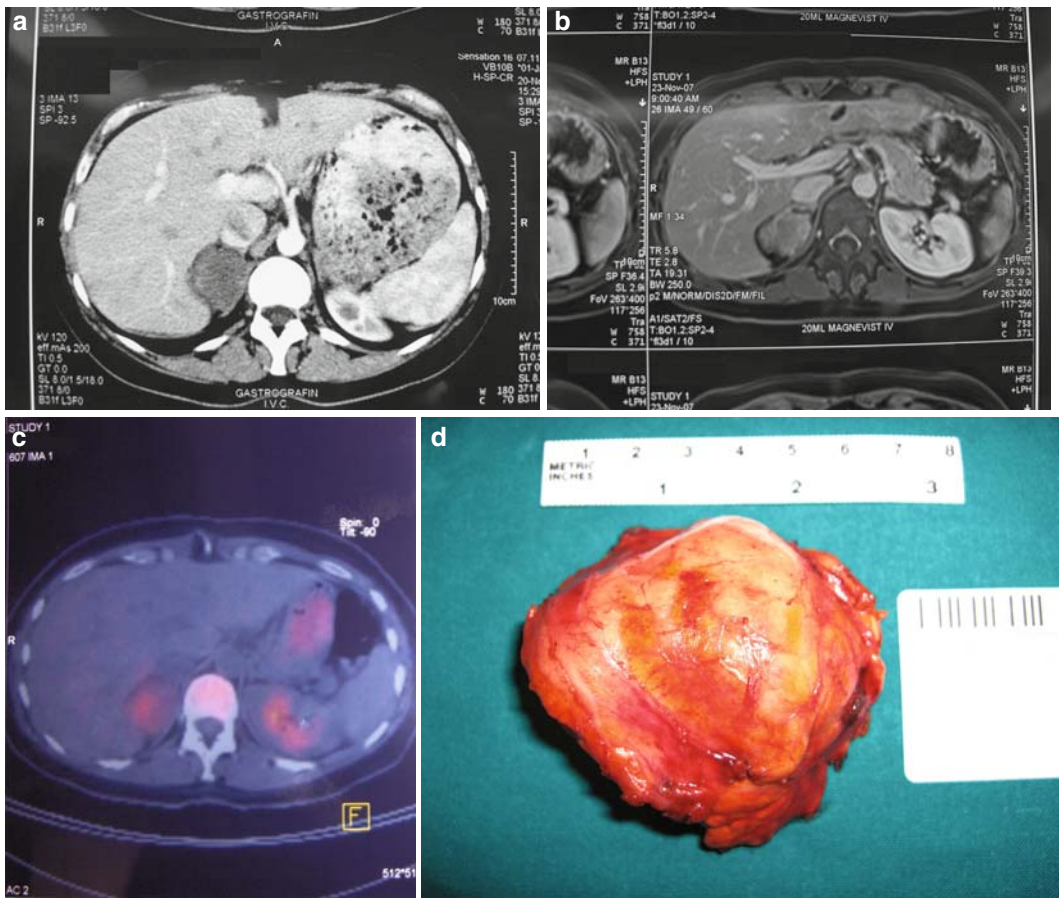

Fig. 31.4. A 43-year-old wf (white female) with a history of bilateral mastectomies for extensive in situ lobular breast carcinoma 18 months ago. Currently a right adrenal incidentaloma is discovered. (**a**) CT of a 5-cm right adrenal mass (30 units of Hounsfield). (**b**) MRI appearance of the same lesion. (**c**) 18F-FDG-PET scan with increased metabolic function (SUV max 4) in the right adrenal indicating metastatic lesion. (**d**) The gross specimen (6.7 × 6.4 cm in diameter) that eventually proved to be a benign ganglioneuroma.

of metastasis (synchronous or metachronous) and/or local invasion into adjacent structures. The mapping and identification of genes responsible for hereditary syndromes (e.g., multiple endocrine neoplasia type 1, Li-Fraumeni) have increased our understanding of adrenocortical tumorigenesis. Oncogenes and tumor-suppressor genes involved in adrenal carcinomas include mutations in the p53 tumor-suppressor gene. Amongst those, the Ki67 index (% immunopositive cells) when above 5% can be a useful indicator in the differentiation of adenomas from carcinomas [54]. Adrenal carcinomas are monoclonal, whereas adrenal adenomas may be polyclonal in approximately 25–40% of cases [55, 56]. Although these findings do not have direct clinical application, it is hoped that future research will facilitate the diagnosis and predict the natural course of these tumors.

Management of Adrenal Incidentalomas: Surgery Versus Follow-Up

The management of adrenal incidentalomas remains controversial despite the commissioned systematic review of the literature at the state of the science conference sponsored by the National Institute of Health [58, 59].

Several recent studies demonstrated that:

1. A relatively high percentage of adrenal incidentalomas, especially adrenal cortical adenomas, are subclinically functioning.
2. A relatively high percentage of patients with adrenal incidentalomas display pathological features, such as impaired glucose tolerance, insulin resistance, increased blood pressure, high triglyceride levels, low HDL, central fat deposition, and reduced trabecular bone mineral density.
3. When adrenalectomy was done in patients who either had proven subclinical hypercortisolism or had even truly nonfunctioning tumors, the associated abnormalities and symptoms (such as hypertension, obesity, and altered glucose tolerance) were normalized or significantly improved.

In the era of laparoscopic adrenalectomy that carries a minimal morbidity and mortality, it appears logical to advocate surgery in patients with adrenal incidentalomas when

1. There is laboratory evidence for a subclinically functioning tumor
2. There are associated pathological features such as hypertension, impaired glucose tolerance (or diabetes), pathological triglyceride profile, central fat deposition, reduced bone mineral density
3. There is clinical and radiological evidence of primary or solitary metastatic adrenal carcinoma.

The age and the anxiety of the patient should also play a role in the decision to operate or not. Conservative management is recommended of those patients with adrenal incidentalomas in whom: (1) There is no clinical or laboratory evidence for subclinical function of the tumor, (2) there are no associated symptoms potentially related to the adrenal incidentaloma, and (3) there is no suspicion of adrenal carcinoma. In these patients a yearly checkup should be continued for 5–10 years with the main emphasis on the possibility that the silent, nonfunctioning tumor may subsequently develop hyperfunction.

Complete though limited follow-up studies (with repeated radiologic and hormonal evaluation) have been performed on patients with adrenal incidentalomas. A multicenter Swedish prospective study including 229 patients with incidentaloma published controversial results after a median follow-up of only 2 years. They reported an increase in size in 7.4% and hypersecretion in 2% during this time. No cancer was detected although only 79% of the patients not primarily adrenalectomized were followed with CT [57]. Barzon and associates [60] followed 75 patients with adrenal incidentalomas, observed them for a median of 4 years, and found nine adrenal incidentalomas to have enlargement. Overt Cushing's syndrome developed in two patients, subclinical Cushing's syndrome in three, and clinical pheochromocytoma in one. No patient had a malignancy. The estimated cumulative risks for mass enlargement and hyperfunction were 18 and 9.5%, respectively, after 5 years, and 22.8 and 9.5% after 10 years. In another study [61], 53 patients with adrenal incidentalomas were followed for 6–78 months (medium 24 months). During the follow-up, 22 lesions (41.5%) increased in size and 6 lesions (11.3%) decreased in size or disappeared. No adrenal incidentaloma grew or developed hypersecretion. Thus, during follow-up of the truly nonfunctioning adrenal incidentaloma, yearly hormonal evaluation rather than repeating imaging studies for size monitoring should be emphasized.

What is the Best Surgical Approach in the Management of Adrenal Incidentalomas?

Traditionally, surgical approaches to the adrenals have been anterior transperitoneal, posterior extraperitoneal, and thoracoabdominal (for large tumors) [62]. The application of laparoscopic techniques in surgery of the adrenal glands has essentially replaced all traditional open approaches in the same manner that laparoscopic cholecystectomy has replaced traditional open cholecystectomy. Because there are so many benefits associated with the laparoscopic approach, open adrenalectomy should be reserved for the large/potentially malignant tumors or documented adrenocortical carcinomas invading the surrounding tissues. We have compared the anterior, posterior, and laparoscopic approach in 165 patients who underwent adrenalectomy between 1984 and 1994 [63]. Although in this study we included our early

cases and learning experience, the advantages of the laparoscopic approach were clearly shown in terms of morbidity (12.2% in the anterior approach, 8.1% in the posterior approach, and 0% in the laparoscopic approach), mean operating time, mean length of postoperative hospitalization (8.1 days vs 4.5 days vs 2.7 days), and minimal postoperative pain. The lack of long incisions and their immediate and long-term complications (e.g., wound infection, hernia, esthetic dissatisfaction) and the opportunity for an early return to full activity make the laparoscopic approach the procedure of choice for nearly all adrenal incidentalomas, including the laparoscopically removable primary or secondary carcinomas [31, 64] (Fig. 31.3). The anterior (or lateral) laparoscopic adrenalectomy enables the removal of large tumors, the performance of additional procedures (e.g., cholecystectomy), and the performance of bilateral laparoscopic adrenalectomies when indicated [65, 66]. The laparoscopic approach is used in almost all adrenal masses independent of the size with the exception of the adrenal carcinoma infiltrating the surrounding tissues as seen on preoperative imaging studies. There is always the possibility to convert the laparoscopic approach to a hand-assisted laparoscopic adrenalectomy [7] or an open adrenalectomy if needed (see Chapter 33). Recently the posterior retroperitoneal adrenalectomy that was introduced and standardized by M. Waltz [67] offers additional advantages such as avoidance of intraabdominal adhesions, no need for mobilization of intraperitoneal organs and easier direct access to the adrenal especially is obese patients. It appears to be a faster procedure especially in the case of bilateral adrenalectomy [68].

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32

Adrenal Metastases and Rare Adrenal Tumors

Arsalla Islam and Fiemu E. Nwariaku

Introduction

With the improved sensitivity of hormonal assays and safety of laparoscopic adrenalectomy, the outcomes for patients with functioning, nonmalignant adrenal tumors are excellent. Benign (nonfunctioning) adrenal adenomas and metastases however comprise the most common incidentally – discovered tumors of the adrenal gland. Adrenal metastases are present in approximately 27% of postmortem examinations of patients with malignant neoplasms of epithelial origin [1, 2]. Primary neoplasms of the lung, breast, melanoma, kidney, and gastrointestinal tract are most commonly associated with adrenal metastases [1–3]. Lung cancer and melanoma represent the most common tumor types associated with adrenal metastases. Autopsy series have reported adrenal gland metastases in 10–59% of patients with non-small-cell lung cancer [1, 4]. Adrenal metastases are found in 50% of cases of malignant melanoma [5]. This very high incidence was also shown in another series of 216 patients where 46.8% had either unilateral or bilateral adrenal metastases [6]. This study demonstrated that the adrenal gland is the sixth most common site of distant metastases from melanoma [after lymph nodes (73.6%), lungs (71.3%), liver (58.3%), brain (54.6%), and bone (48.6%)]. This series also showed that the incidence of adrenal metastases from malignant melanoma was threefold that of colorectal carcinoma. Also, the adrenal gland is the second most common site of metastasis from hepatocellular carcinoma [7].

The declining mortality rates for patients with these primary tumors portend a situation where metastases in general and adrenal metastases in particular will become more common. These metastases are also likely to be discovered earlier because of more frequent surveillance, and more sensitive imaging techniques such as positron emission tomography (PET). Hence, there is a need for better understanding of the issues associated with the management of such patients, especially the choice of biochemical and imaging tests and appropriate therapy.

Most metastases to the adrenal gland are discovered during surveillance imaging in patients with a personal history of cancer. Kloos and colleagues reported that 32–72% of incidentally discovered adrenal masses in patients with a history of cancer were metastases [8]. Others have found similar rates, reporting that about half of adrenal masses in 91 patients with a recently diagnosed extra-adrenal malignancy were metastatic, whereas 48% were primary adrenal lesions, including pheochromocytoma and cortical adenomas [9]. The median duration from diagnosis of the primary cancer to the identification of adrenal metastases is approximately 2.5 years, although adrenal metastases have been discovered up to 22 years after initial treatment of primary tumors [10].

These observations suggest that hormonal evaluation should precede other imaging or

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biopsy in patients with a personal history of malignancy and an incidental adrenal mass. Decisions regarding adrenalectomy in patients with a nonfunctioning adrenal mass can then be based on factors such as the presence of other sites of metastases, the patient's medical status, and the predicted survival rate from their primary malignancy. Adrenalectomy in this context is associated with prolonged survival, albeit in a highly selected group of patients. Furthermore the laparoscopic approach has been shown to be safe in this patient population. In this chapter, we discuss the evaluation of patients with adrenal metastases. In particular, we review the biochemical evaluation, imaging techniques, and indications for adrenalectomy. A discussion of rare adrenal tumors is also included to provide insight into the management of these uncommonly encountered tumors.

Biochemical Evaluation

Almost half of the adrenal tumors identified in patients with a personal history of malignancy are biochemically functioning. Therefore, the appropriate biochemical evaluation of these patients is necessary to guide therapeutic decisions. All patients should undergo biochemical evaluation for cortical and medullary hyperfunction prior to further imaging, biopsy, and treatment. In the largest series of incidental adrenal masses, which included 1,096 cases over a 15-year period, the majority of tumors (74%) were nonsecretory adenomas, whereas 14.8% were hypersecretory and 4% were primary adrenal carcinomas. Among the hypersecretory tumors, 9.2% were cortisol-secreting adenomas, 4.2% were pheochromocytomas, and 1.4% were aldosteronomas [11]. However, Lenert et al. demonstrated that about half of adrenal masses in patients with a personal history of extra-adrenal malignancy were metastatic, whereas 48% were primary adrenal lesions [9].

We previously described a preferred algorithm for the biochemical evaluation of adrenal hyperfunction [12], Tests of cortical and medullary hyperfunction should include 24-h measurements of urinary free cortisol (UFC) and a dexamethasone suppression test, as well as plasma or urinary metanephrine measurements. These sensitive biochemical tests are detailed in Table 32.1.

The normal range of UFC in most assays is between 220 and 330 nmol/24 h (80–120 μg/24 h) [13]. Although it is a highly sensitive test, there are occasional problems with adequacy of urine collection and cross-reactivity with exogenous glucocorticoids. These can be prevented by giving patients adequate written instructions [14]. There remains a small but finite false-negative rate. One study found a false-negative rate of 5.6% and a false-positive rate of 3.3% in combined data from 479 individuals [15]. Expressing UFC over creatinine allows the adequacy of

Table 32.1. Biochemical evaluation for cortical and medullary hyperfunction

	Biochemical study	Sensitivity and specificity	References
Tests of adrenal cortical function	24-h urinary free cortisol	Sensitivity: 100% Specificity: 98%	Mengden T, et al. [17]
	1 mg dexamethasone-suppression test	Sensitivity: 97–100%	Yanovski JA [18] Hankin ME [19] Kennedy L [20]
	Plasma aldosterone activity to renin ratio (PAC:PRA > 30 + PAC > 20 ng/dl)	Sensitivity: 90% Specificity: 91%	Weinberger MH, et al. [22]
Tests of adrenal medullary function	24-h urinary metanephrines	Sensitivity: 98%	Lenders JW [23]
	Plasma metanephrines	Sensitivity: 97–100%	Eisenhofer G [25]

collection to be established and improves the specificity [16], although it should be noted that creatinine may vary with changes in lean body mass. In another study [17], UFC measurement was shown to have a diagnostic sensitivity and specificity of 100 and 98%, respectively.

Using radioimmunoassays for serum cortisol measurement has improved test sensitivity to about 97–100% [18–20].

Screening for the adrenal cortical hyperfunction should also include the measurement of plasma aldosterone concentration (PAC) and estimation of plasma renin activity (PRA) to exclude primary aldosteronism (PA). In addition to documenting an elevated ratio of plasma aldosterone to PRA (>20), an elevated plasma aldosterone should be present (>15 ng/dl) [21]. For the diagnosis of PA, a PAC to PRA ratio of >30 plus a PAC >20 ng/dl is associated with a sensitivity and specificity of 90 and 91%, respectively [22].

Plasma metanephrines or 24-h urinary metanephrines have a reported sensitivity in the range of 97–100% [23–26]

Imaging Adrenal Metastases

Computerized Tomography Scan

Abdominal computerized tomography (CT) scan is the preferred method for assessing the size and characteristics of adrenal masses. CT is fast, readily available, and offers the highest spatial resolution. Adrenal adenomas are usually small, well-defined homogeneous lesions with clear margins and large intralesional lipid content. Large tumor size, irregular shapes, vague contour, invasion into surrounding structures, and high values on nonenhanced CT are suggestive of malignancy [27]. Incidental adrenal lesions are now found in up to 5% of scans.

Benign adrenal masses consist predominantly of intracellular lipid (composed mainly of cholesterol, fatty acids, and neutral fat), whereas malignant lesions contain less intracytoplasmic fat. This property has been used to differentiate adenomas from nonadenomas on CT and magnetic resonance imaging (MRI) scans. Such intralesional fat can be quantified by low attenuation values [Hounsfield units (HU)] on nonenhanced CT in patients with benign adenomas. Both CT and MRI can reliably characterize intralesional fat content. There is an inverse linear relationship between the intracytoplasmic fat content of an adrenal adenoma and the CT attenuation value measured as Hounsfield units [28]. Nonadenomatous lesions have higher CT density values because their cytoplasm is relatively lipid-poor. A CT scan attenuation value <10 HU or visual detection of a diffuse decrease in relative signal intensity (SI) (relative to spleen) suggests a lipid-containing benign adenoma with a specificity of more than 95% and a sensitivity of nearly 80% [29]. Although rare, metastases have uncommonly been reported in lesions that measure less than 10 HU [30].

An analysis of pooled data from 10 studies recommended 10 HU as a reasonable cutoff to differentiate benign from nonbenign tumors [29]. This low threshold although sensitive is not very specific. However this may be an acceptable trade off to prevent the misdiagnosis of a malignant adrenal tumor as benign. A limitation of this approach is that most adrenal masses are of intermediate density (10–40 HU) range, which would lead to further diagnostic tests in most patients. Furthermore, most routine abdominal CT scans are performed with intravenous contrast, thus rendering interpretation of density values difficult. In order to minimize these limitations, the rate of contrast washout has been used as a surrogate to differentiate benign from malignant masses. The rate of washout of intravenous contrast agents is slower in nonadenomas compared with adenomas. Korobkin et al. [31] note that adenomas washout rates were 51% at 5 min and 70% at 15 min, with sensitivity and specificity of 96%. In another study of 78 lesions [32], all benign adrenal adenomas had density measurements less than 37 HU, whereas all nonadenomas had density measurements greater than 41 HU, 30 min after intravenous contrast administration. Another study [31] showed that no malignant lesions had a density of less than 25 HU at a 15-min delay. This allows for 100% specificity with only minimal interruption of the patient flow in the CT scanner. As such we recommend the use of dedicated CT protocols with washout analyses in the evaluation of incidental masses. Our adrenal CT protocol uses 2-mm noncontrast, dynamic (60 s) images, followed by 10 min delayed imaging through the adrenals. Figures 32.1–32.3 show bilateral adrenal metastases in a patient with

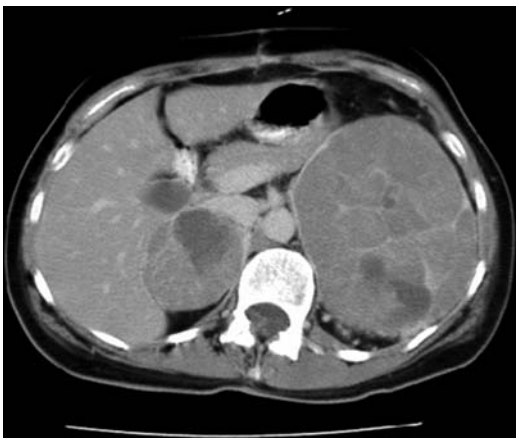

Fig. 32.1. Bilateral adrenal metastases in a patient with metastatic melanoma.

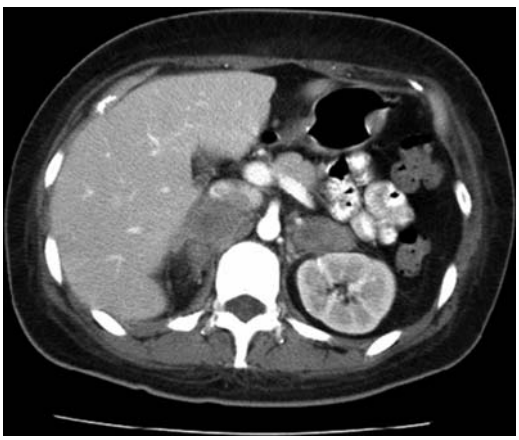

Fig. 32.2. Lymphoma metastasis to the adrenal gland.

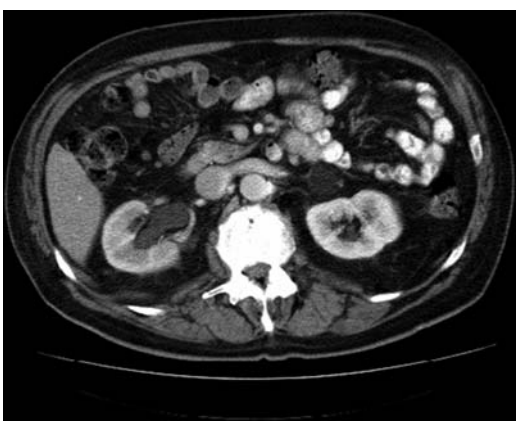

Fig. 32.3. Adrenal metastasis in a patient with unknown primary carcinoma.

metastatic melanoma, metastasis from lymphoma, and from unknown primary malignancy, respectively.

Magnetic Resonance Imaging

MRI also exploits the intralesional fat content to exclude malignancy. With the advent of dynamic gadolinium-enhanced and chemical-shift imaging (CSI), MRI has become a very useful diagnostic method in the characterization of adrenal masses. The chemical-shift MRI technique is used often with demonstrated sensitivity of 81–100% and specificity of 80–100% for differentiating adenomas from nonadenomas [33–37]. Korobkin et al. [38] and Outwater et al. [39] showed that the presence of histologic lipid in many of the examined adenomas accounted for the low attenuation on unenhanced CT, causing a loss in SI on chemical-shift MRI. The low attenuation values of adenomas on nonenhanced CT and the lower SI in opposed phase compared to in-phase MRI result from intratumoral fat content [38–41]. Adrenal MRI should include T1-weighted axial images for anatomic detail and T2-weighted axial images [41]. Fat suppression is useful to prevent degradation of heavily T2-weighted images by periadrenal fat. MRI also has the added advantage of avoiding patient exposure to radiation and is useful in patients with allergy to iodine-containing contrast media. Both CT and MRI are useful in excluding malignancy within an adrenal lesion; however, they fall short of confirming adrenal malignancy. The definitive diagnosis of malignancy usually requires percutaneous biopsy or surgical pathology. However, noninvasive imaging can reduce the need for percutaneous biopsy of adrenal lesions found in oncologic patients [42, 43].

Positron Emission Tomography

PET is now the most common imaging technique for surveillance of patients with a history of malignancy [44]. As such, many incidental adrenal lesions in oncology patients are initially discovered on PET scan. The most commonly used technique uses fluorodeoxyglucose (FDG/PET), which relies on uptake of FDG by metabolically active cells as a method of identifying metastatic lesions. PET has high sensitivity for identifying adrenal lesions; however, the specificity for malignant adrenal masses is poor [44–47]. In an

effort to avoid false-positive results from adrenal adenomas (which also take up FDG to a varying degree), some have modified the PET criteria for a malignant lesion. Yun et al. [44] defined lesions with subjective uptake (SUV) greater than or equal to the liver as positive for metastasis and less uptake than the liver as negative. Using these criteria, they reported 100% sensitivity and 94% specificity in 50 adrenal lesions. In the rare cases in which an adrenal adenoma does show elevated metabolic activity on PET, the activity may reflect inflammation within the lesion [48]. Several studies also highlight that the addition of CT scan to PET has improved the sensitivity for detection of malignant lesions [49, 50]. FDG/PET is unable to distinguish adrenal cortical carcinoma (ACC) from metastatic disease in the adrenal glands. Nor can it reliably diagnose pheochromocytomas, metastatic disease, and lymphomas, which generally exhibit high glycolytic activity [51].

Percutaneous Biopsy

Although adrenal biopsy is of limited utility in patients with incidentally discovered adrenal masses, CT-guided adrenal biopsy is an important diagnostic tool in patients with a personal history of extra-adrenal malignancy. Cytologic evidence of adrenal tissue excludes metastatic adrenal malignancy and prevents unnecessary evaluation and patient anxiety, whereas a biopsy result positive for malignancy facilitates therapeutic planning in patients with no evidence of other metastases. Percutaneous fine-needle aspiration (FNA) biopsies of the adrenal gland that demonstrate malignancy have a positive predictive value of 100% and a negative predictive value for malignancy of 92% [52]. Complication rates vary from 8 to 13%, although most are mild and self-limiting [53, 54]. The overall sensitivity of core biopsy for malignancy is reported 99% and the specificity as 96% [52]. However post-procedure bleeding is more common with core biopsies. It is imperative to exclude adrenal medullary hyperfunction prior to biopsy, so as to avoid hemodynamic and vascular complications such as severe hypertension, myocardial infarction, or cerebrovascular incidents. There are also reports of tumor seeding of the needle tract [55].

Management of Adrenal Metastases

The appropriate management of adrenal metastases depends on the type and extent of the primary malignancy, patient comorbidity and disease-free interval (DFI, the interval between diagnosis of the primary malignancy and the recognition of the adrenal metastases). Figure 32.4 serves as a guideline in the management of adrenal metastases. Since adrenalectomy is usually not curative, one must balance the risk of surgery with potential benefit of prolonging the time to recurrence.

Of all the outcome predictors in adrenal metastases, DFI may be the most predictive. Synchronous lesions are described as metastases that are recognized within 6 months of the primary malignancy (DFI less than 6 months), while metachronous lesions are recognized more than 6 months after diagnosis of the primary tumor. Surgery and chemotherapy have been shown to increase survival in synchronous adrenal metastases from lung cancer [56]. Metachronous metastases are extremely rare, possibly because of the short life span of patients with lung cancer [57]. In a review of 18 solitary metachronous adrenal metastasis (15 unilateral, 3 bilateral), identified in patients with operable nonsmall-cell lung cancer between 1965 and 1999, the median interval between pulmonary resection and treatment of adrenal lesion was 11.5 months. The median survival after adrenalectomy and postoperative chemotherapy was 19 months, compared with 15 months after chemotherapy alone, 14 months after adrenalectomy alone, and 8 months after palliative radiation therapy.

There is now evidence that resection of isolated adrenal metastases may offer a survival benefit [56, 58, 59]. Kim et al. [60] and Lo et al. [58] recommend aggressive treatment in patients who undergo complete resection of the primary lung tumor and have a DFI more than 6 months. Adrenal metastases from lung cancer and melanomas represent the bulk of these patients. Kim et al. conducted a retrospective review of 37 patients who had undergone adrenalectomy for metastatic disease at their institution between 1986 and 1996. Five-year survival was 24%. DFI >6 months and complete resection were the only predictors of

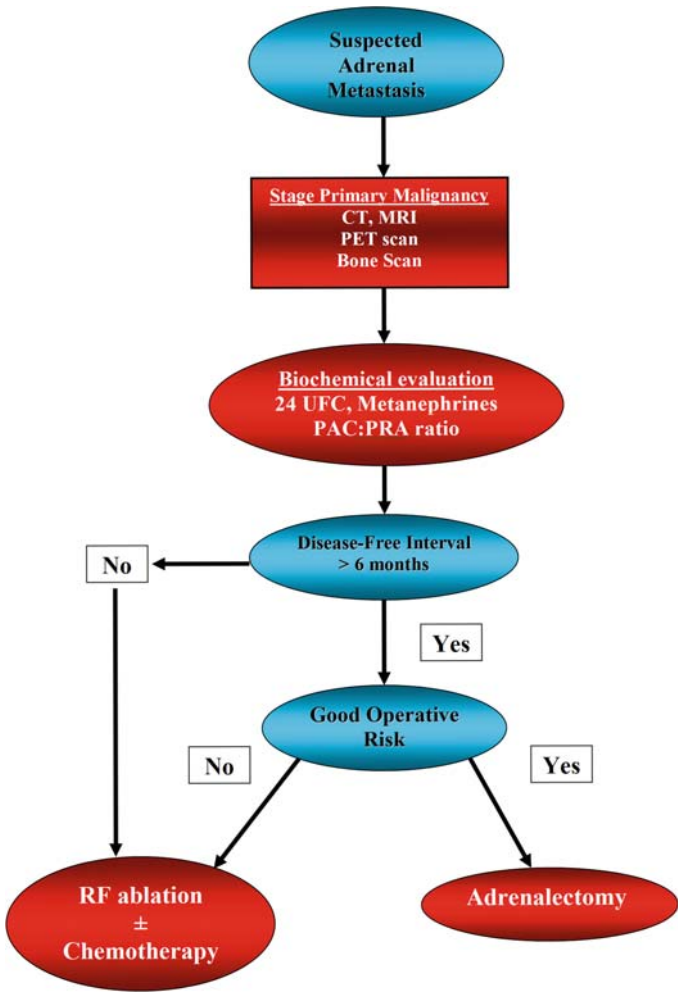

Fig. 32.4. Flowchart for management of adrenal metastases.

improved survival. Lung cancer was the most common primary tumor, followed by renal and colorectal cancer [60]. Sarela et al. [61] with a retrospective review of 41 patients who underwent adrenalectomy during 1997–2002 at this institution showed an overall 5-year survival of 29%.

Mercier et al. described the management of 23 patients, who underwent complete resections of solitary adrenal metastasis after surgical treatment of nonsmall-cell lung cancer. The diagnosis of adrenal metastasis was synchronous with the diagnosis of nonsmall-cell lung cancer in 6 of the 23 patients and metachronous in 17 patients. The median DFI for the patients with metachronous adrenal metastasis was 12.5 months (range 4.5–60.1 months). The overall 5-year survival of these 23 patients was 23% after adrenalectomy for solitary adrenal metastasis. Univariate and multivariate analysis showed that a DFI greater than 6 months was an independent and significant predictor of increased survival in patients after adrenalectomy. All patients with a DFI of less than 6 months died within 2 years of the operation. In contrast, the 5-year survival rate was 38% after resection of a solitary adrenal metastasis that developed more than 6 months after lung resection. Findings from other studies also support the concept that a DFI less than 6 months

and synchronous metastasis were associated with significantly worse survival rates and suggested either tumor aggressiveness or advanced tumor stage that was undetected when the primary lung carcinoma was resected [62]. Luketich and Burt reported a much better median survival (31 months) in patients with synchronous metastases after neoadjuvant chemotherapy and adrenal resection than did Mercier and associates. Other factors, such as the T and N staging of the primary tumor, histology, administration of adjuvant therapy, or size of the metastases, did not affect survival.

A retrospective study of 24 patients with melanoma metastatic to the adrenal glands [63] showed that eight patients underwent resection for cure, two patients underwent partial resection of large unilateral adrenal metastases, and 14 patients with unresectable tumors had chemotherapy or were treated symptomatically. Mean survival in the group that underwent resection for cure was 59 months (with four of the eight patients living more than 5 years), whereas survival in the unresectable group was 15 months. An important caveat is that many of these studies consist of highly selected patients; therefore these results may not be easily extrapolated to all patients with adrenal metastases. We could find no convincing evidence supporting adrenalectomy for patients in whom the source of the primary malignancy is unknown.

Technique of Adrenalectomy

Open adrenalectomy has been the preferred surgical approach in patients with primary or metastatic adrenal cancer. This technique ensured en bloc excision of tumor by the tumor. However complication rates associated with open adrenalectomy are high. With increasing laparoscopic experience many surgeons now advocate laparoscopic adrenalectomy for metastases and malignant lesions of the adrenal gland [64]. In selected patients laparoscopic adrenalectomy can be performed in the absence of local invasion [65]. Patients who require a more radical excision may be best served by open adrenalectomy [66]. Although laparoscopic resection of large tumors (>15 cm) has been reported [67], this is more technically challenging because of the limited visibility, increased vascularity, and the difficulty with manipulation and retraction of a large tumor. Therefore many surgeons still recommend open adrenalectomy for very large tumors.

In a retrospective review of 170 patients comparing laparoscopic and open adrenalectomy for ACC [68], tumor fracture occurred during attempted bag extraction in one patient, while another patient underwent open conversion due to uncontrolled hemorrhage. There are at least two independent reports of the rapid development of peritoneal carcinomatosis after laparoscopic adrenalectomy for ACC [69, 70]. On the other hand, a number of studies show that laparoscopic adrenalectomy is associated with minor postoperative discomfort, reduced hospital stay, and reduced complication rate [71–74]. Some authors report no port site metastases or loco-regional recurrences after long-term follow-up of patients who underwent laparoscopic adrenalectomy for malignant tumors [75, 76]. Despite favorable results from major centers, several isolated cases of local tumor recurrence have been reported by other groups. The recurrences developed in conjunction with the appearance of metastases at other sites in the body; however, in some cases, the pattern of recurrence suggested that tumor spread was by the laparoscopic dissection, pneumoperitoneum, or both [69, 77, 78].

Sarela et al. [61] performed a retrospective study on 41 patients undergoing open or laparoscopic adrenalectomy for adrenal gland metastases. The overall 5-year survival rate was 28 months. The size of the adrenal metastases removed by laparoscopic adrenalectomy was significantly smaller than those removed by the open approach (median diameter 4.5 vs 7.4 cm). The authors found that a DFI exceeding 6 months was the only significant predictor of improved survival. Taken together, these results suggest that well-selected patients with adrenal metastases can safely undergo laparoscopic adrenalectomy with no oncological disadvantage [65, 66, 79].

Ablation of Adrenal Metastases

Given the palliative nature of interventions for adrenal metastases it is not surprising that attempts have been made to ablate these lesions operatively or percutaneously. CT-guided radiofrequency ablation may be the most popular technique, especially in patients who are poor surgical candidates [80, 81]. Both

the adrenal mass and the location of the RF electrode are reliably seen on CT [81]. Radiofrequency ablation uses alternating RF current to generate heat and induce tissue necrosis. RF electrodes placed in the tumor cause local ion agitation and heat to cause local tissue destruction. There is minimal morbidity associated with this procedure and the follow-up imaging and biochemical results indicate that RF ablation effectively destroys both native adrenal tissue and adrenal metastases, particularly those smaller than 5 cm in diameter [81]. RF treatment can also be performed on an outpatient basis with minimal morbidity [81, 82]. Alpha and beta blockers may be considered in patients undergoing RF ablation of adrenal lesions to avoid hypertensive crisis as this has been reported as a complication of RF performed on a liver metastasis adjacent to a normal adrenal gland [81]. Other palliative techniques include selective arterial embolization and injection of alcohol or acetic acid.

Rare Adrenal Tumors

Adrenal Hemorrhage

Focal or diffuse adrenal hemorrhage is seen in 0.1–1.1% of autopsy cases [83]. Adrenal hemorrhage commonly occurs in association with trauma [84], surgery [85], anticoagulant therapy [86], septicemia [87], hypotension, or tumor (metastases, carcinoma, pheochromocytoma, or adenoma). In such cases, bilateral adrenal hemorrhage usually develops and acute adrenal insufficiency is clinically present [88]. Increased adrenocorticotropic hormones have been implicated in adrenal hemorrhage, and there are reports of adrenal hemorrhage in patients with inflammatory bowel disease treated with intravenous adrenocorticotropic hormone. Animal studies confirm that adrenocorticotropic hormones cause the adrenal glands to enlarge and become hyperemic, eventually leading to necrosis and hemorrhage [89]. Other mechanisms for adrenal hemorrhage include stress or adrenal medullary venous thrombosis [90–93]. Adrenal hemorrhage is best managed by correcting clinically – evident coagulopathy and replacing blood components as necessary. These lesions are usually self-limiting. Hemorrhagic pseudocysts are the most common adrenal cysts.

Adrenal Cysts

Adrenal cysts are rare with an incidence of less than 0.1% [94]. They comprise 4–22% of adrenal incidentalomas [8].The most common presentation is an incidentaloma; however, some patients may also develop abdominal pain and mass [95]. Adrenal cysts may be benign or malignant. The endothelial cysts are lymphangiomatous or angiomatous. These are small and multiple. The epithelial cysts are most likely derived from embryonic rests and include cystic adenomas, embryonal cysts, and glandular retention cysts. The benign adrenal cysts have a reported incidence at autopsy of 0.064–0.18% [96]. With the advent and widespread use of imaging cystic diseases of the adrenal gland are being found more frequently today. Due to its low incidence there are few reports of laparoscopic management of adrenal cysts [97, 98].

Adrenal cysts are more common in women and in patients in fourth and fifth decade of life [99]. Although most adrenal cysts are nonfunctioning and asymptomatic, they can become large enough to cause nonspecific abdominal or flank pain, or hypertension [100, 101]. Pseudocysts often arise from hemorrhage within the adrenal gland, sometimes secondary to stress, birth, trauma, and surgery. Adrenal cysts can also occur in association with benign and malignant tumors. The overall incidence of malignancy in adrenal cysts is estimated to be about 7% [95].

For adrenal cysts 5 cm or greater confirmed by the imaging or smaller ones in which malignancy is suspected, a complete endocrine evaluation is recommended [102]. It should include serum potassium, renin, cortisol, and 24-h urinary catecholamines, metanephrines, vanillylmandelic acid, 17-hydroxycorticosteroids, and aldosterone. Small, asymptomatic, or nonfunctioning cysts can be followed clinically without intervention [103].When adrenal cysts are 6 cm or greater, symptomatic or functioning or malignancy is suspected on imaging, surgical removal is recommended [103]. Surgical intervention can be open [104] with cyst enucleation or en bloc adrenalectomy, or laparoscopic [97, 105, 106] with cyst decortication and adrenalectomy.

While the endothelial cysts have been reported to be the most common subtype of adrenal cysts in some reports [107], there is evidence that adrenal pseudocysts are more common in three different reports [103]. The separation into endothelial cysts and pseudocysts might be clinically insignificant since some pseudocysts are believed to represent endothelial cysts which have lost the endothelial lining [108].

Lymphangioma

Lymphangiomas represent 16% of all adrenal cysts. They are usually asymptomatic and small, and discovered incidentally during abdominal imaging for other reasons. Cyst wall calcification may also be present. No intervention is necessary if the cyst is simple and has no solid component and if the patient is asymptomatic. Adrenalectomy is indicated if the cyst enlarges or if the patients develop symptoms related to the cyst.

Pseudocysts

A pseudocyst lacks an epithelial lining and often is a result of hemorrhage or infarction. An adrenal pseudocyst is a cystic lesion arising within the adrenal gland that is surrounded by a fibrous tissue wall devoid of a recognizable lining layer. Calcification in the wall of a cyst is suspicious for a pseudocyst or a parasitic cyst. An adrenal tumor can also undergo cystic degeneration and form a pseudocyst. Adrenal cysts may become secondarily infected. Surgical excision is recommended in the presence of symptoms or if there is suspicion of malignancy.

Parasitic Infections

Hydatid cyst can present as a cyst in relation to the adrenal gland. Serology for Echinococcus is performed for diagnosis. Most sensitive screening tests are ELISA and indirect hemagglutination tests. Detection of antibody to Echinococcal antigen and a CT showing peculiar morphology of daughter cysts will confirm the diagnosis. Aspiration is not recommended if parasitic cyst is suspected because of the risk of dissemination or anaphylaxis [109]. Adrenalectomy with care to avoid disruption of the cyst is the treatment of choice.

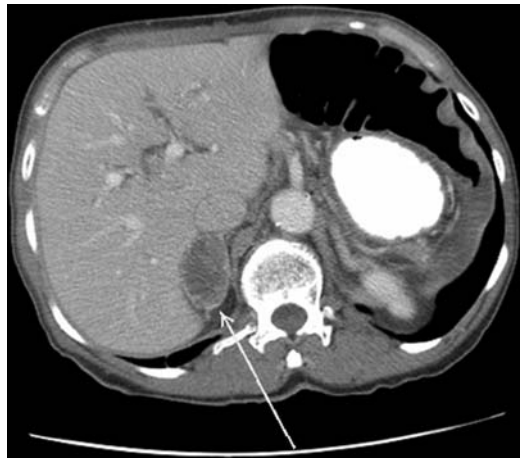

Fig. 32.5. Myelolipoma of the right adrenal gland.

Myolipomas

Adrenal myolipomas are rare tumors (0.08–2% of the population), benign, nonfunctional, and asymptomatic. Symptomatic cases often manifest with abdominal pain attributable to spontaneous rupture of the mass, intratumoral hemorrhage, or compression of peritumoral tissues [110]. The presence of the fat in the tumor is the key to the diagnosis of the myelolipoma. Currently, there is no consensus regarding the appropriate management of adrenal myelolipomas. Surgical removal is indicated for symptomatic lesions or if malignancy is suspected [110]. Figure 32.5 demonstrates myelolipoma of the right adrenal gland.

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33

Technique of Open and Laparoscopic Adrenalectomy

Dina M. Elaraj and Quan-Yang Duh

Introduction

Evaluation of an adrenal mass is one of the most unique and interesting problems in the field of surgery. It entails determining whether the adrenal mass is functional or nonfunctional, benign or malignant, and primary (i.e., arising within the adrenal gland) or metastatic from another site. The work-up consists of biochemical testing, imaging studies, and, rarely, invasive testing such as selective venous sampling. In the case of a nonfunctional adrenal mass, patients should undergo age- and gender-appropriate risk factor-screening tests in order to exclude common malignancies. Rarely, in the case of a patient with a history of cancer or in the case of a patient with bilateral adrenal masses, a fine-needle aspiration biopsy (after excluding the possibility of pheochromocytoma) may be necessary.

Indications for adrenalectomy are listed in Table 33.1. Details regarding the work-up of a patient with an adrenal mass or the diagnosis of patients with functioning adrenal tumors are found in Chapter 31. The present chapter is focused on the various techniques of adrenalectomy.

Preoperative Preparation

The preoperative preparation of the patient depends on the results of the hormonal testing as well as the clinical and biochemical diagnosis. In addition to the usual steps taken to prepare a patient for a major operation, patients with functional tumors require special consideration.

Pheochromocytoma

Preparation for surgery in a patient with pheochromocytoma consists of alpha blockade for 1–3 weeks before operation. The most commonly used agent is phenoxybenzamine, a long-acting alpha adrenergic antagonist. In addition, if the patient has a history of arrhythmias, or if after adequate alpha blockade the patient experiences persistent tachycardia or extra-systoles, a beta blocker is added. The most commonly used agent is propranolol. In addition, because patients with pheochromocytomas tend to have intravascular volume depletion due to chronic vasoconstriction, volume expansion is an essential part of the preoperative preparation [1]. Furthermore, as 25–75% of patients with pheochromocytoma may have impaired glucose tolerance [2], appropriate blood glucose control is also important.

Aldosteronoma

Since all patients with aldosteronoma have hypertension, appropriate blood pressure control is important. Patients usually require multiple agents to control their blood pressure. Most

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Table 33.1. Indications for adrenalectomy

Functional Tumors
Pheochromocytoma
Conn's syndrome (aldosteronoma)
Cushing's syndrome
Cortosol-secreting adenoma
Bilateral adrenal hyperplasia
Ectopic adrenocorticotropic hormone (ACTH) syndrome
Pituitary-dependent Cushing's disease unsuccessfully managed by transsphenoidal surgery
Virilizing/feminizing tumors
Adrenocortical carcinoma
Nonfunctional Tumors
Incidental adrenal mass (incidentaloma) >3–4 cm or increasing in size
Isolated metastasis from another site
Symptomatic cyst or angiomyolipoma
Adrenocortical carcinoma

patients are also hypokalemic, and preparation for surgery includes replenishing total body potassium stores using potassium, spironolactone, a competitive aldosterone antagonist in the distal tubules of the kidney, or both [3].

Cushing's Syndrome

Preparation for surgery in a patient with Cushing's syndrome requires treatment of the metabolic effects of excess cortisol secretion. This includes management of hypertension, excellent blood glucose control, and correction of electrolyte disturbances. In the case of patients who require bilateral adrenalectomy for the treatment of their disease [e.g., those with ectopic adrenocorticotropic hormone (ACTH) syndrome, those with bilateral adrenal hyperplasia, or those with pituitary-dependent disease unsuccessfully managed by transsphenoidal surgery], preoperative ketoconazole, a cytochrome p450 inhibitor that inhibits various steps of steroid biosynthesis, is given to decrease cortisol secretion [4, 5].

Operative Approach

Adrenalectomy can be performed via an open or laparoscopic approach. The most common open techniques include the anterior (transabdominal), flank, and posterior (retroperitoneal) approaches, with the thoracoabdominal approach usually reserved for large and/or invasive tumors. Laparoscopic approaches similarly include the transperitoneal or retroperitoneal approach.

The decision as to whether to perform an open or laparoscopic adrenalectomy depends on many factors, including preoperative suspicion for malignancy, presence of local invasion into surrounding structures, tumor size, and surgeon experience. Since the first laparoscopic adrenalectomy was done in 1992 by Gagner and colleagues [6], it has become the preferred approach in most circumstances. Multiple studies have demonstrated the advantages of the laparoscopic approach, including less operative blood loss, fewer postoperative complications, decreased requirement for parenteral analgesics, faster resumption of regular diet, decreased length of hospital stay, and faster return to regular activities [7–11].

Because most adrenalectomies today are performed via the laparoscopic approach, its technique will be discussed first. Open adrenalectomy is sometimes necessary for large or invasive tumors, and details specific to an open dissection will then be discussed.

Anatomic and Technical Considerations

The adrenal glands are paired structures located in the retroperitoneum, superior to the kidneys. The differences in surrounding structures between the right and the left adrenal glands are well-known, and details regarding exposure and dissection will be given in the following sections.

One of the most vital anatomic details to remember is the difference in blood supply between the right and the left sides. While the arterial blood supply is similar on both sides, the venous drainage is very different. The arterial blood supply consists of the superior adrenal artery (from the inferior phrenic artery), the middle adrenal artery (from the aorta), and the inferior adrenal artery (from the renal artery). These arteries are frequently not discrete vessels and their branches are usually easily controlled with electrocautery.

The venous drainage consists of one dominant vein that must be ligated or clipped, with

smaller accessory veins that follow the arteries and can usually be controlled with electrocautery. Of note, in patients with larger tumors, very vascular tumors, or obviously malignant tumors, these accessory veins can become very large and may require ligation or clips as well. The right adrenal vein is very short, and drains into the posterolateral aspect of the inferior vena cava (IVC), while the left adrenal vein is longer, and drains into the left renal vein. Of note, the left inferior phrenic vein is usually seen medial to the left adrenal vein, and it joins the left adrenal vein before its junction with the left renal vein. Identification and control of the adrenal veins is one of the most important (and sometimes one of the most challenging) parts of adrenalectomy.

Intraoperative Considerations

As adrenalectomy is done under general anesthesia, all patients should receive perioperative deep vein thrombosis (DVT) prophylaxis. Only those with Cushing's syndrome require preoperative antibiotics, which should be effective against gram-positive organisms. Patients with Cushing's syndrome should also receive preoperative stress-dose glucocorticoids [12]. A Foley catheter should be placed.

In addition to the standard monitors and equipment, some patients require special additional considerations. Despite adequate alpha ± beta blockade, patients with pheochromocytomas can have wide swings in their blood pressure during surgery, and thus should have an arterial line and central venous catheter placed, with medications readily available to control hypo- or hypertension. Patients with obviously invasive and malignant tumors, in whom en bloc resection of adjacent organs is planned, should similarly have an arterial line and central venous catheter. In addition, for patients in whom IVC invasion and/or tumor thrombus is seen or suspected, vascular instruments and preparation for venovenous bypass may be necessary. As with the planning of any operation, anticipation of potential complications and preoperative preparation for those will ensure that the operation proceeds as safely and as smoothly as possible.

Technique of Laparoscopic Adrenalectomy

Laparoscopic adrenalectomy may be performed via a transabdominal (transperitoneal) or posterior (retroperitoneal) approach, with the transperitoneal approach performed more commonly. Advantages of the transperitoneal approach include more familiar anatomy and the ability to do a general abdominal exploration. Advantages of the retroperitoneal approach include direct access to the adrenal gland with decreased need for intraabdominal dissection. Major limitations of this approach, however, are the difficulty in converting to an open procedure in the case of a vascular injury, and that the small working space only allows resection of tumors measuring 5–6 cm or smaller. Multiple studies have demonstrated the safety and efficacy of both techniques, with both retrospective and prospective randomized studies showing no difference between the two techniques with respect to operative time, blood loss, postoperative analgesic requirement, length of stay, or time to return to normal activities [13–16]. In addition, a cost analysis model similarly showed no difference between the techniques [17]. Thus, which technique to choose depends on surgeon preference, which may be influenced by tumor size, presence of bilateral tumors, or history of previous abdominal surgery.

Laparoscopic Transabdominal (Transperitoneal) Adrenalectomy

Patient, Equipment, and Surgeon Position

Laparoscopic transperitoneal adrenalectomy can either be done with the patient in the supine (referred to as the anterior approach) or in the lateral decubitus position (referred to as the lateral approach). The anterior approach has the advantage of being able to do a bilateral adrenalectomy without having to reposition the patient; however exposure of the adrenal gland is more difficult using this approach.

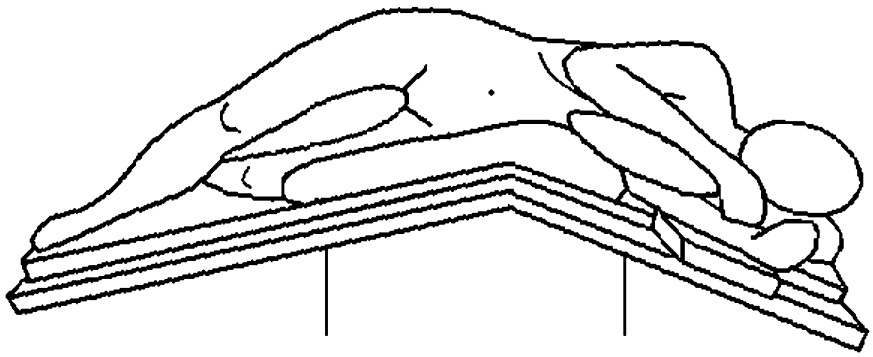

Fig. 33.1. Patient position for laparoscopic transperitoneal right adrenalectomy via the lateral approach. The patient is placed in the right lateral decubitus position on a gel-covered beanbag, with the break in the table located at or just cephalad to the costal margin.

The lateral approach has the advantage of being able to use gravity to retract the liver on the right, and the spleen and tail of pancreas on the left. Because of this significant advantage and because the lateral approach is more commonly used, this approach will be described, with our modifications of the original technique reported by Gagner and colleagues [6, 7, 18].

The patient is positioned on the operating room table in the lateral decubitus position (with side of the adrenal pathology facing up) on a gel-covered beanbag, with the break in the table located at or just cephalad to the costal margin (Fig. 33.1). The arm closest to the table is extended on an armrest, with the other arm supported with pillows or on another elevated armrest. An axillary roll is placed. The leg closest to the table is flexed, the other leg straight, and pillows placed between them. All pressure points should be well-padded.

The table is then flexed, the kidney rest raised, the patient positioned at about 80° (10° posterior lean), and suction applied to the beanbag. Take care to not allow the beanbag to be too close to the anterior abdominal wall, as this may limit excursion of the abdomen during insufflation. The patient should be taped to the table in three places: over the lower extremities, over the hip, and over the chest. The table should then be tilted in multiple directions to make sure that the patient does not move. Taking the extra time required for proper positioning is essential for the smooth performance of the operation.

The patient is prepared and draped from beyond the umbilicus to the spine, and from below the iliac crest to the nipple. Video monitors are placed at the patient's head, and the surgeon and assistant stand on the side facing the patient's abdomen.

Equipment

A list of recommended equipment is given in Table 33.2. Laparoscopic adrenalectomy is performed using three or four trocars, which may be 10–12 or 5 mm in size, depending on the size of the camera, fan retractor, dissecting instruments, clip-applier, and other preferred equipment, such as an ultrasonic shear or electrothermal bipolar tissue-sealing device. A 30° angled laparoscope is essential. A fan retractor is useful

Table 33.2. Recommended instruments for laparoscopic adrenalectomy

One or two video monitors
Three or four 10–12 or 5 mm trocars
30° angled laparoscope (10 or 5 mm)
Two blunt, atraumatic bowel graspers
Fan retractor
Hook cautery
Suction and irrigation device
Medium-large clip-applier
Ultrasonic shear or electrothermal bipolar tissue sealing device
Tightly rolled X-ray detectable gauze sponges (cigarette sponges)
Impermeable nylon bag

to retract the liver during right adrenalectomy, and sometimes helpful to retract the spleen during left adrenalectomy. X-ray detectable gauze sponges tightly rolled-up like a cigarette are very helpful for blotting and retracting, but can only be placed through a 10-mm or larger port. A laparoscopic ultrasound probe (5–7.5 MHz) is helpful in select cases, such as in an obese patient in whom a small adrenal tumor is lost in the retroperitoneal fat, or when the adrenal venous anatomy is unclear [19]. A thick impermeable nylon bag is used to remove the specimen from the patient.

Right Adrenalectomy

Four trocars are placed about 2 cm below the right costal margin as shown (Fig. 33.2). The medial-most trocar, placed first at the lateral border of the rectus muscle, should be a 10-mm port through which the fan retractor will be placed. The abdomen is insufflated to 15 mm Hg, and the abdomen is visually explored. The lateral-most trocar is placed next at the costovertebral angle under direct vision. The remaining two trocars are placed such that the spacing between the four ports is equal and maximal. The camera is inserted through the second port, hook cautery through the third port, and an atraumatic bowel grasper through the lateral-most port.

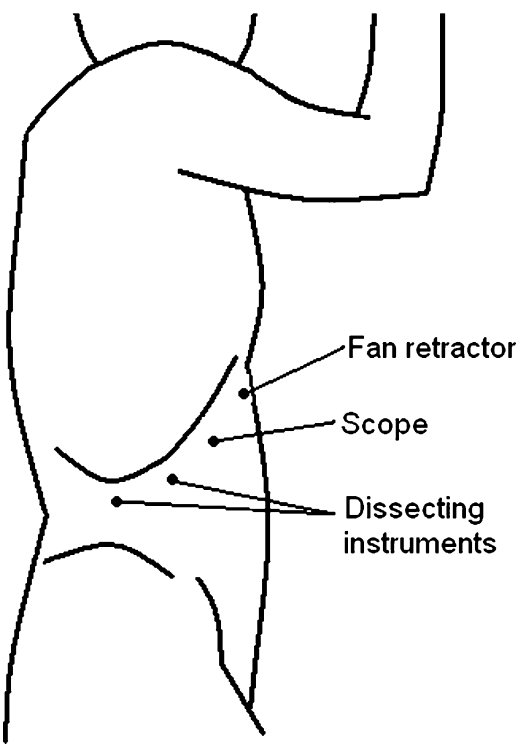

Fig. 33.2. Trocar position for laparoscopic transperitoneal right adrenalectomy.

The first step involves mobilizing the liver and opening the space between the liver and the retroperitoneum just like opening the pages of a book. The fan retractor is used to retract the liver medially. The lateral attachments of the liver and right triangular ligament are then taken down using the hook cautery, allowing the liver to rotate medially, and exposing the right adrenal tumor and IVC. The dissection extends cephalad all the way up to the diaphragm, taking care to avoid injuring the diaphragm and causing a pneumothorax. This is most prone to happening in patients with Cushing's syndrome due to the friability of their tissues. It is very rare to need to mobilize the hepatic flexure of the colon in order to get further exposure.

The next step involves mobilization of the adrenal gland itself. This dissection is initially done in a top-down manner: the superomedial aspect of the gland and its surrounding periadrenal fat is dissected away from the liver, proceeding in a cephalad to caudad manner, until the muscles of the retroperitoneum are seen. It is helpful to hold a tightly rolled X-ray detectable gauze sponge in the grasper of the left hand to provide lateral traction. The small vessels off the inferior phrenic artery and vein identified during this part of the dissection can generally be cauterized. This initial dissection creates a "V" shaped opening "unzipping" the superomedial aspect of the adrenal gland from the liver, so the dissection can proceed from cephalad to caudad toward the adrenal vein.

As the dissection moves to the inferomedial aspect of the gland and the liver is mobilized and retracted away from the adrenal gland, the lateral aspect of the IVC is identified and gently dissected away from the medial aspect of the adrenal gland. The right adrenal vein will be encountered and should be carefully dissected circumferentially, then clipped with at least two clips on the IVC side before being transected. Be aware that once its main venous drainage is interrupted, the

adrenal gland can become engorged and the dissection can become more bloody, particularly for tumors such as pheochromocytomas. Meticulous attention to hemostasis is essential.

Once the adrenal vein is taken, the next step is to dissect the gland away from the renal hilum. At this stage of the dissection, we usually use a blunt grasper to lift the adrenal cephalad from the renal hilum by insinuating it between the inferolateral aspect of the adrenal and the kidney near the upper edge of the hilum. Retracting the adrenal gland away from the renal hilum facilitates the dissection of the inferior adrenal artery branches, and most importantly helps identify and avoid injuring a possible superior pole branch of the renal artery. A small superior pole renal artery branch can easily be mistaken for the inferior adrenal artery, and injury to this artery can result in renal vascular hypertension.

Once the adrenal gland is safely dissected away from the renal hilum, the remainder of the dissection involves separating the adrenal tumor from the upper pole of the kidney, and then dividing its superolateral and posterior attachments. This part is done last, as these attachments greatly aid in holding the adrenal gland in place during all of the previous dissection. Here, again we use a grasper placed between the kidney and the adrenal to hold the adrenal gland up, and we use either an ultrasonic shear or electrothermal bipolar tissue sealing device to complete the dissection. The surface of the upper pole of the kidney is usually seen at the completion of this dissection.

The specimen including adrenal tumor and surrounding periadrenal fat should then be placed in an impermeable nylon bag and removed from the patient. This can be done either by breaking up the tumor and removing it piecemeal through the 10- to 12-mm port, or by extending the skin and fascial incision of one of the port sites. The dissection bed should then be inspected to assure hemostasis, the ports withdrawn under direct vision, and the fascia and skin closed in the standard fashion.

Left Adrenalectomy

Trocar size and position is identical to that of right adrenalectomy, although the left side can be done with three ports (if desired, omit the medial-most port) rather than four if one can get good medial retraction of the spleen and tail of pancreas using gravity. We prefer four ports because it is often helpful to use an atraumatic grasper or fan retractor to retract the spleen and tail of pancreas medially.

The first step in this dissection involves mobilizing the spleen and tail of pancreas and, similar to right adrenalectomy, opening the space between the spleen and the retroperitoneum just like opening the pages of a book. Exposure begins by mobilizing the splenic flexure of the colon inferiorly using the hook cautery and retracting it inferiorly away from the kidney. The splenorenal ligament is then incised along the lateral border of the spleen, and the dissection proceeds cephalad to the diaphragmatic attachments and short gastric vessels. It is not necessary to divide the short gastric vessels. The spleen and tail of pancreas can then be easily retracted medially. It is important not to dissect too far laterally and enter the plane posterior to the kidney.

The next step of the dissection is very similar to that of right adrenalectomy, in that mobilization of the left adrenal gland begins with a top-down dissection at the superomedial aspect of the gland and proceeds in a cephalad to caudad manner until the muscles of the retroperitoneum are seen. The dissection should continue caudad along the medial aspect of the gland until the left adrenal vein is seen. The left inferior phrenic vein is usually seen first parallel and medial to the medial edge of the adrenal. Once the anatomy of the inferior phrenic vein and the adrenal vein is clearly delineated, the inferior phrenic vein can be clipped and transected. This helps mobilize the adrenal gland superolaterally and makes dissection and ligation of the adrenal vein easier and safer.

After dividing the adrenal vein, the remainder of the operation is identical to that of right adrenalectomy. Again, lifting the adrenal gland away from the renal hilum is important to avoid injuring a possible superior pole renal artery.

Laparoscopic Posterior (Retroperitoneal) Adrenalectomy

The technique of retroperitoneal adrenalectomy was first described by Mercan and colleagues in 1995 [20]. Since that time, several authors have

reported on their series and modifications of the original technique [21, 22].

Patient, Equipment, and Surgeon Position

The patient is positioned on the operating room table in the prone jackknife position, with the back level and the chest and abdomen supported laterally by parallel bolsters, thus allowing for abdominal excursion during insufflation. Video monitors are placed at the patient's head, and the surgeon and the assistant stand at the foot of the bed.

Equipment

In addition to the equipment listed in Table 33.2, additional equipment helpful to perform laparoscopic retroperitoneal adrenalectomy includes transcutaneous ultrasound (with a 3.5- to 5-MHz transducer) and laparoscopic ultrasound (with a 5- to 7.5-MHz transducer), as well as a 10-cm spherical dissecting balloon.

Adrenalectomy

Three trocars are placed below the tips of the twelfth and eleventh ribs as shown (Fig. 33.3). Their exact position is guided by identifying the locations of the ribs, kidney, and adrenal tumor by ultrasound. Prior to preparing and draping the patient, the outline of the twelfth rib is drawn on the patient, as well as the outline of the kidney and adrenal tumor as identified by transcutaneous ultrasound. The initial 12-mm trocar is placed 2 cm inferior and parallel to the twelfth rib, at about the level of the lower pole of the kidney. A 0° laparoscope is then inserted.

The first step is to create a space within Gerota's fascia posterior and superior to the kidney by blunt dissection with the tip of the 0° laparoscope. The trocar is then aimed and advanced to the level of the superior pole of the kidney. The trocar is then withdrawn and replaced with a 10-cm spherical dissecting balloon. The balloon is used to further develop the space. The balloon is then withdrawn, the trocar replaced, and the retroperitoneum insufflated to 20 mm Hg of pressure. This amount of pressure in the retroperitoneum is usually well-tolerated, and greatly aids in maintaining hemostasis during the dissection [22]. The two additional trocars (either 10–12 mm or 5 mm) are placed under direct vision on either side of the first trocar. A 30° laparoscope is then inserted into the medial-most port (closest to the spine) and used for the remainder of the procedure.

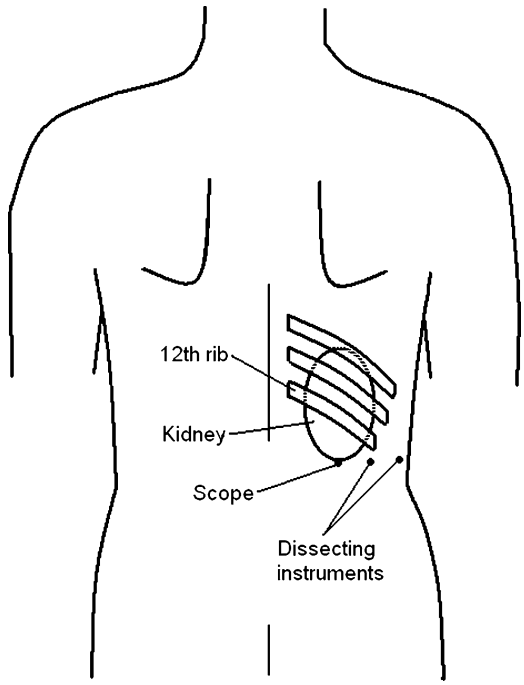

Fig. 33.3. Trocar position for laparoscopic retroperitoneal right adrenalectomy.

The next step involves identification and dissection of the adrenal gland. Laparoscopic ultrasound may be useful to identify the location and extent of the adrenal tumor. The dissection is then done using hook cautery, an ultrasonic shear or electrothermal bipolar tissue sealing device, or bluntly with atraumatic bowel graspers. The dissection commences at the inferior aspect of the gland, separating it from the upper pole of the kidney, which is then retracted caudally. The dissection then continues along the medial aspect of the gland and proceeds in a cephalad direction. The adrenal vein is encountered and controlled with clips similar to the transperitoneal approach. The superolateral attachments are taken last, as they help hold the adrenal gland in place during the inferior and medial dissection.

Extraction of the tumor and surrounding periadrenal fat, and closure of the fascia and skin incisions are similar to that done in the transperitoneal approach.

Technique of Open Adrenalectomy

As stated above, laparoscopic adrenalectomy has become the gold standard for extirpation of adrenal tumors. However, an open approach is necessary in some circumstances, such as when a tumor is large or there is invasion into neighboring structures. Many have recommended that tumors larger than 6–8 cm in diameter should be approached open, but larger tumors have been resected laparoscopically as long as there are no obvious signs to suggest malignancy [23]. Open adrenalectomy may be done via an anterior (transabdominal), thoracoabdominal, flank, or posterior (retroperitoneal) approach. An epidural catheter is helpful for postoperative pain control.

Anterior (Transabdominal) and Thoracoabdominal Approaches

Patient and Surgeon Position

Patient positioning is similar for the transabdominal and thoracoabdominal approaches. For the transabdominal approach, the patient is placed supine on the operating table with the arms tucked or extended on armboards at the sides. In addition, for the thoracoabdominal approach, the patient should be placed on a beanbag with a shoulder roll placed vertically under the flank of the side of the adrenal tumor. This helps elevate the chest on that side, and allows access to the lateral-most extent of the incision. The arm on the side of the adrenal tumor should be tucked. Surgeon position depends on surgeon preference.

Equipment

Standard equipment and retractors are used to perform open adrenalectomy. As the adrenal tumor is located in the retroperitoneum, a headlight is very helpful. In addition, the thoracoabdominal approach requires equipment necessary to clear and transect a segment of rib, along with a rib spreader for exposure. A double-lumen endotracheal tube is helpful. A vascular set and preparation for venovenous bypass may be necessary. A chest tube and pleurovac are necessary at the end of the case.

Incision

The choice of incision for open transabdominal adrenalectomy depends on tumor anatomy, including size and invasiveness into surrounding structures. Various incisions include vertical midline, extended subcostal [subcostal incision extending superiorly over the xiphoid (sometimes requires cutting the xiphoid with a pair of heavy scissors; can also be extended to a full median sternotomy as an alternative to the thoracoabdominal approach)], bilateral subcostal, and thoracoabdominal.

While the thoracoabdominal incision provides excellent exposure, it may cause more morbidity associated with the opening of two body cavities, more pain, and the potential for other complications such as phrenic nerve injury during division of the diaphragm [24]. The thoracoabdominal incision is planned out over the eighth or ninth rib, extending from the posterior axillary line along the rib and curving over the abdominal wall toward the umbilicus. The abdominal part of this incision should be made first, and the peritoneal cavity explored for metastatic disease. If none is found, then the thoracic part of the incision can be continued. The latissimus dorsi, serratus anterior, and intercostal muscles are divided. The cartilaginous costal arch is transected. The pleura is entered along the superior aspect of the rib (remember that the neurovascular bundle runs just inferior to the rib). A periosteal elevator is used to clear the rib, and an approximately 4-cm segment of rib is removed to allow for exposure. The diaphragm is divided in a circumferential fashion along its periphery. It is helpful to place marking sutures every 2–3 cm on either side of the divided diaphragm in order to help align it during closure. A rib spreader can then be inserted to provide exposure.

Right Adrenalectomy

Similar to laparoscopic right adrenalectomy, the first step involves mobilizing the liver medially

and superiorly by taking down the lateral attachments and right triangular ligament. In contrast to laparoscopic adrenalectomy, further exposure of the adrenal gland is obtained by reflecting the hepatic flexure of the colon inferiorly, and performing a Kocher maneuver of the duodenum to expose the IVC. If there is concern about invasion into adjacent organs, en bloc resection of the kidney or part of the liver may be necessary. If there is concern for invasion of or tumor thrombus in the IVC, vascular control of the supra- and infra-hepatic IVC should be obtained before commencing dissection of the tumor. Note that in addition to the adrenal vein, large and/or invasive tumors may have multiple large parasitic blood vessels that also need to be ligated. Figure 33.4 shows an example of a 13.5-cm right adrenocortical carcinoma that required en bloc nephrectomy for resection.

Left Adrenalectomy

There are two approaches to the left adrenal gland. Similar to the laparoscopic approach, the left adrenal tumor may be exposed by reflecting the splenic flexure of the colon inferiorly, and mobilizing the spleen and tail of pancreas medially. A second approach involves entering the lesser sac by dividing the gastrocolic ligament in its avascular plane. The peritoneum inferior to the pancreas is then incised, followed by incising Gerota's fascia, and then reflecting these structures superiorly. This infra-pancreatic approach dissects a smaller space and is suitable mainly for smaller and more inferiorly positioned tumors. Sometimes both dissections are necessary in order to obtain good exposure. Again, if there is concern about invasion into adjacent organs, en bloc resection may be necessary.

Closure

Each surgeon has his/her own preferred method for closure. A variety of types and sizes of suture may be used. A subcostal incision should be closed in two layers (anterior and posterior rectus sheath). If a thoracoabdominal incision was used, a chest tube should be placed and the diaphragm reapproximated using a running or

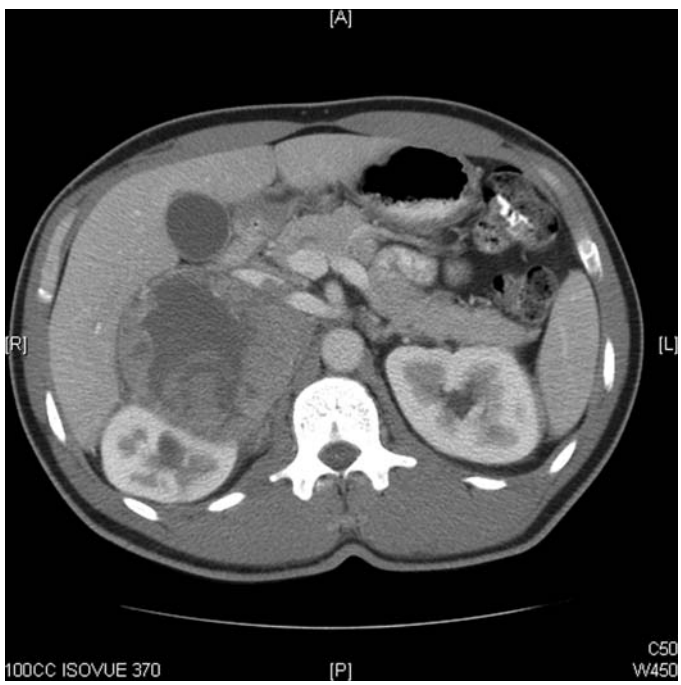

Fig. 33.4. Computed tomography scan of a patient with a 13.5-cm right adrenocortical carcinoma whose resection also required en bloc nephrectomy via a thoracoabdominal approach.

interrupted monofilament suture. The previously placed marking sutures help align the two sides. In order to take tension off the diaphragmatic closure, the costal cartilage should be reapproximated using either a heavy monofilament suture or a stainless steel wire before completion of the diaphragmatic closure. The ribs should then be approximated with interrupted heavy monofilament or Tevdek sutures, followed by closure of the serratus anterior and latissimus dorsi muscles in two layers.

Flank and Posterior (Retroperitoneal) Approach

The flank and open posterior retroperitoneal approaches are not commonly performed, as large and/or invasive tumors should be resected via a transabdominal or thoracoabdominal approach, and smaller tumors that would be amenable to these approaches should be resected laparoscopically. Thus, these techniques will not be discussed.

Postoperative Care

The postoperative care of a patient who has undergone adrenalectomy depends on the operative approach, extent of resection, and functional or nonfunctional nature of the tumor. For patients who have undergone laparoscopic or open adrenalectomy without en bloc resection of adjacent organs, the postoperative care is routine, consisting of pain control, continuation of DVT prophylaxis, and early ambulation. A nasogastric tube is unnecessary and can be removed in the recovery room. Patients who have undergone laparoscopic adrenalectomy may have a general diet as tolerated immediately. Those who have undergone open adrenalectomy may have a postoperative ileus, and may take a day or two before they are ready for a general diet. Patients with functional tumors require special considerations.

Pheochromocytoma

Because patients with pheochromocytomas can have hemodynamic instability postoperatively, they should be monitored in the postanesthesia or intensive care unit for a minimum of 4 h before being transferred to a regular ward. Alpha blockade should be discontinued. If beta blockade was given preoperatively, it should be continued and weaned postoperatively. Studies examining the role of perioperative beta blockade in patients undergoing noncardiac surgery (not specific to pheochromocytomas) vary in the duration of postoperative therapy from 2–30 days after surgery [25, 26].

Aldosteronoma

Similar to patients with pheochromocytoma, all antihypertensive medications except beta blockers should be discontinued in patients who have undergone adrenalectomy for aldosteronoma. Spironolactone should be discontinued, and the patient's serum potassium checked the morning after surgery. Blood pressure should be checked as an outpatient, with reinstitution of one or more additional antihypertensive medications if necessary.

Cushing's Syndrome

Patients with Cushing's syndrome should receive prophylactic antibiotics and stress-dose glucocorticoids perioperatively [12]. Because the function of the contralateral adrenal gland will be suppressed, these glucocorticoids will need to be continued postoperatively, to be tapered over the next several months. Mineralocorticoid replacement is only necessary if the patient has undergone bilateral adrenalectomy. Blood glucose control usually improves after the operation.

Summary

In summary, laparoscopic adrenalectomy has become the gold standard approach for patients requiring this operation, and may be done via a transperitoneal or retroperitoneal approach. Large and/or invasive tumors that may require en bloc resection are approached via the open transabdominal or thoracoabdominal approach. The postoperative care of these patients depends on operative approach, extent of resection, and functional nature of the tumor.

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Laparoscopic Retroperitoneal Adrenalectomy

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Introduction

Laparoscopic adrenalectomy has largely replaced open adrenalectomy as the preferred method for resection of most adrenal tumors. Adrenocortical cancer and malignant pheochromocytoma remain relative contraindications to this rule. Over the years, many techniques for laparoscopic adrenalectomy have been developed, including multiple variations on the transabdominal and retroperitoneal approaches (i.e., lateral, supine, prone). The lateral transabdominal approach has become the most widely used technique for laparoscopic adrenalectomy due to the familiar view and well-defined anatomical landmarks while the retroperitoneal approaches fell by the wayside at most centers. However, in recent years a number of advances in the posterior retroperitoneal technique have led to a renaissance in the laparoscopic retroperitoneal approach for selected patients.

Since the first case report of successful retroperitoneal adrenalectomy in 1994, the technique of this operation has been significantly improved and refined to the point where some authors consider it superior to the lateral transabdominal approach for selected patients [1]. In fact, some institutions use the retroperitoneal approach as the preferred method of adrenalectomy for most adrenal tumors. In the largest series to date, Walz et al. performed 560 adrenalectomies via this approach in tumors that spanned the gamut of pathology and size up to 10 cm [2]. In the early phases of development, the main problems with the retroperitoneal approach included (1) difficulty creating an adequate working space and (2) lack of traditional landmarks. Many of these issues were solved by optimizing the patient positioning, increasing the retroperitoneal insufflation pressure, and codifying the approach to dissection [3–5]. In particular, the liberal use of insufflation pressures of 12–30 mm Hg have drastically increased the size of the working space and made the operation much simpler.

Benefits of Retroperitoneal Adrenalectomy (Compared to Transabdominal Adrenalectomy)

Reduced Operating Times

Many series have documented that operative times for laparoscopic adrenalectomy by any method have reached parity with open operative times and in most cases have decreased [7–9]. While the duration of operation differs between the left and the right side, the average operative time for a lateral transabdominal approach is approximately 80–120 min. In the largest series of retroperitoneal adrenalectomies, the average operative time was 67 min [2]. When the analysis was limited to the most recent operations,

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this operative time dropped even further to 40 min, reflecting the steep learning curve of the early years of development. Much of this decrease in operative time between the two methods is due to the direct access to the adrenal gland in the retroperitoneal technique. With the transabdominal technique, much of the operation is spent mobilizing the abdominal viscera (i.e., liver, spleen, pancreas) just to expose the adrenal gland. In the retroperitoneal approach, the kidney, adrenal gland, and periadrenal fat are immediately in view with little dissection. In addition, one of the most time-consuming parts of the procedure is proper patient positioning. For cases of bilateral adrenalectomy, obviating the need to "flip" the patient into the contralateral decubitus position in the lateral transabdominal approach further reduces operating room time. With the retroperitoneal approach, the patient need only be shifted toward the contralateral side of the table.

Avoidance of Intraabdominal Adhesions and Irradiated Fields

Laparoscopic lateral transabdominal adrenalectomy is safe and feasible to perform in patients who have had prior abdominal surgery. However, in a large multicenter retrospective analysis there was a trend toward longer operative times in patients with previous upper abdominal surgery [6]. The retroperitoneal technique eliminates the need for lysis of intraabdominal adhesions, further reducing operative time. With the exception of certain urologic procedures, the retroperitoneal planes are seldom affected by previous operations. The same benefit applies for avoiding the desmoplastic reaction in previously irradiated fields.

Potential Decrease in Postoperative Pain and Incisional Hernia

In general, laparoscopic adrenalectomy has reduced the incidence of complications, length of stay, and severity of postoperative pain when compared to open adrenalectomy [10, 11]. Some authors have suggested that retroperitoneal adrenalectomy yield further decreases in postoperative pain then even the laparoscopic transabdominal approach, although this has yet to be proven in a randomized controlled clinical trial [2, 12]. In addition, incisional hernia rates in laparoscopic transabdominal adrenalectomy depend largely on the pathology and whether or not the surgeon enlarges the fascia at the site of extraction. However, incisional hernias are almost nonexistent with the retroperitoneal approach since the kidney occupies the space through which potential hernias would encroach.

Improved Hemostasis

One of the side benefits of insufflation in a small, closed space is that the increased pressure leads to improved hemostasis. The small venules and arterioles associated with the adrenal gland typically "auto-tamponade" and seal with insufflation pressures alone at pressures of 12–20 mm HG. If there is recalcitrant bleeding, often increasing the insufflation pressure to 25–30 mm Hg will effect hemostasis. In one large series, when a caval injury or adrenal vein injury occurred, increasing the insufflation pressure allowed for hemostasis until a definitive solution was accomplished. Of note, there were no instances of gas embolism in this series [6].

Disadvantages of Retroperitoneal Adrenalectomy (Compared with Transabdominal Adrenalectomy)

The main weaknesses of the retroperitoneal approach include a small working space, a perceived lack of anatomic landmarks, and the inability to explore the rest of the abdominal cavity. As mentioned previously, using increased insufflation pressures and proper positioning of the patient help to enlarge the limited working space. However, judicious selection of patients based on tumor size is critical. Tumors greater than 7 cm in size should be approached through a transabdominal approach. Perhaps the major drawback for the surgeon just learning the technique of retroperitoneal adrenalectomy is the lack of familiar landmarks, such as the spleen, pancreas, and liver. However, once the surgeon is oriented to the layout of the retroperitoneal space, finding the critical landmarks is straightforward. The retroperitoneal space is bounded by the peritoneum laterally, paraspinous muscle medially, ribcage posteriorly (i.e., away from the table), and kidney/adrenal gland/peritoneum anteriorly (i.e., toward the table).

Indications and Contraindications

The indications for laparoscopic retroperitoneal adrenalectomy are generally the same as for laparoscopic transabdominal adrenalectomy. Almost any tumor that can be removed via a transabdominal approach can be removed through the retroperitoneal approach, including pheochromocytoma and adrenal metastases [2, 13–16]. Relative contraindications to a retroperitoneal approach include:

1) Tumors larger than 7 cm – it can be difficult to create an adequate working space with a tumor this large
2) Body mass index >45 – in morbidly obese patients, it is often difficult to create enough room between the table and the patient to accommodate the large pannus. In these situations, the pannus and intraabdominal fat push on the retroperitoneal space, collapsing it.
3) Increased ocular pressures – prone positioning can increase the intraocular and intraorbital pressures and cause pressure on the optic nerve and in extreme cases blindness. This effect is typically only seen in operations lasting many, many hours.
4) Need to explore the rest of the abdomen (such as examining the liver for metastases).

Whether or not suspected adrenocortical cancers or malignant pheochromocytoma should be removed laparoscopically by any means is a controversial topic. With increased experience and laparoscopic skill, the once inviolate rule of removing adrenal cancers through an open incision has been challenged. As with other areas where laparoscopy seems to improve oncologic outcomes, laparoscopic resection of primary adrenal cancers may become the norm. One of the few remaining absolute contraindications for abdominal laparoscopy is a disorder that precludes abdominal insufflation (e.g., severe lung or cardiac disease). However, with the limited intrusion on the diaphragm that results from retroperitoneal insufflation, this limitation is only relatively applicable to the retroperitoneal technique. Certainly contraindications to increased venous pressure or decreased venous return (such as cranial hypertension) still apply for retroperitoneal right adrenalectomy since the inferior vena cava is compressed, but may not apply to retroperitoneal left adrenalectomy. Giebler et al. studied the hemodynamic changes with retroperitoneal insufflation and found that hemodynamic changes do occur (increased central venous pressure, cardiac output, mean arterial pressure, and mean pulmonary arterial pressure), but that these changes had no apparent adverse effects [17]. The one absolute contraindication for laparoscopic retroperitoneal adrenalectomy is uncorrectable coagulopathy.

Technique

Patient Positioning

The patient is first intubated on a stretcher and intravenous access and monitoring is obtained as appropriate. A urinary catheter is inserted. Two noncompressible bolsters are placed on the operating table of sufficient size to allow the pannus to lay elevated off the table. One bolster is placed at the joint in the bed where the lower extremity section meets the lower torso section. The hips will rest on this bolster. The second bolster is placed approximately at the level of the lower ribcage. Leg extensions are secured to the table. The patient is then placed in the prone position on the operating table with the hips and chest on the appropriate bolster. The patient should be flush to the side of the table. At this point, it is important to insure that the pannus is elevated off the table and that the bolster does not compress the breasts. The bed is then flexed at the junction of the upper and lower torso sections (approximately 30°) and at the junction of the lower torso and lower extremity sections (approximately 45°) to position the lower back in a completely horizontal position. It is crucial to have the lower back in a completely neutral position to allow for full expansion of the retroperitoneal space. The leg extensions are then positioned horizontal to the floor to help prevent the patient from slipping caudally on the table. The arms are flexed at the elbows. All pressure points are padded generously and the skin is protected while the patient is appropriately secured in place (see Fig. 34.1).

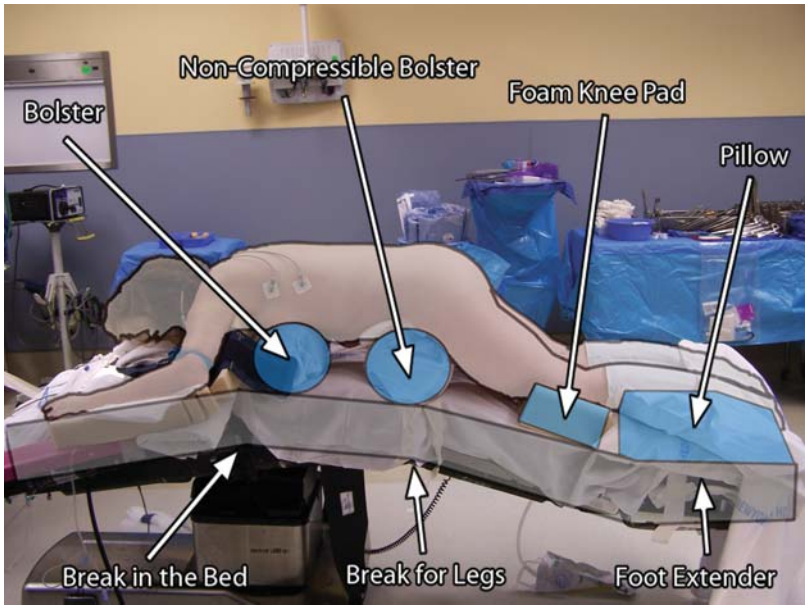

Fig. 34.1. Patient positioning.

Port Placement

Three ports are placed in a rough line based on the inferior costal margin. The middle most port is placed just lateral to the paraspinous muscles and the lateral port is placed as far laterally as possible. These ports are 5-mm ports that are placed under direct palpation. The middle port lies halfway between the lateral and the medial ports and is the first port placed. This port is placed by first making a 1.5-cm incision just inferior to the costal margin and then bluntly entering the retroperitoneal space with a Metzenbaum scissor. Spreading with the scissors expands this site of entry. Using a finger, the retroperitoneal space is then developed bluntly both medially and laterally so that the remaining ports may be placed safely using direct palpation. The medial port incision is placed approximately 4–5 cm caudal to the inferior margin of rib 12. The port is then placed into the retroperitoneal space on a bias or angle just inferior to rib 12. A 10-mm port with a "donut" balloon is placed into the middle port site.

Dissection of the Retroperitoneal Space

After insufflation to a pressure of 15 mm Hg, the camera is introduced into the medial port and using a grasper in the lateral port, the Gerota's fascia is entered bluntly. Once Gerota's fascia is entered, the peri-adrenal and peri-renal fat should be swept anteriorly (i.e., toward the table) staying in the filmy posterior attachments. This dissection is carried laterally to reveal the peritoneum, medially to uncover the paraspinous muscles, and toward the apex where the paraspinous muscle and peritoneum meet. Once the medial port site is free of surrounding tissue, the camera is moved to this port and another instrument is introduced into the medial port. At this point, the superior pole of the kidney is identified. Starting laterally, the connections between the adrenal gland and the superior pole of the kidney are divided. This dissection is carried toward the renal hilum and along the cranial half of the anterior surface of the kidney so that the kidney may be retracted inferiorly and medially. This retraction of the kidney facilitates identification and ligation of the adrenal vein. During the course of this dissection, inferior adrenal arteries may be encountered and should be ligated with a purpose-made sealing device or electrocautery if the vessel is small enough. The filmy plane between the adrenal gland and the paraspinous muscles medially should be dissected with

careful blunt and sharp dissection to expose the inferior phrenic vein on the left and the inferior vena cava on the right. During the course of this dissection, middle and superior adrenal arteries may be encountered and should also be ligated and divided.

Identification and Ligation of the Adrenal Vein

Right Adrenalectomy (Fig. 34.2)

Once the inferior vena cava is identified, the adrenal vein typically enters the adrenal gland at about the midpoint and on its anterior surface (i.e., closer to the table). The adrenal vein may be ligated and divided between clips or with a purpose-made sealing device.

Left Adrenalectomy (Fig. 34.3)

The inferior phrenic vein may be traced toward the renal hilum to identify the adrenal vein. Alternatively, the left adrenal vein may be identified from lateral to medial as the kidney is rotated inferiorly and medially. The left adrenal gland often has a tongue of tissue extending along or caudal to the adrenal vein. It is important to fully dissect out this extension of the gland. The left adrenal vein may be divided in the same manner as the right adrenal vein. The phrenic vein can usually be left intact.

Removal of the Adrenal Gland

Once the adrenal vein is ligated, the adrenal gland may be separated from the filmy attachments to the peritoneum using a combination of blunt and sharp dissection. Staying in this avascular plane facilitates removal of all the periadrenal fat and avoids rupture of the capsule. The specimen is placed in an extraction bag and removed. The 10-mm port site typically does not need to be enlarged to allow for removal. The port is replaced and the retroperitoneal space is inspected under decreased pressure for hemostasis. The ports are removed and the 10 mm port site fascia is closed with an absorbable figure of eight stitch. The skin is closed with subcuticular stitches.

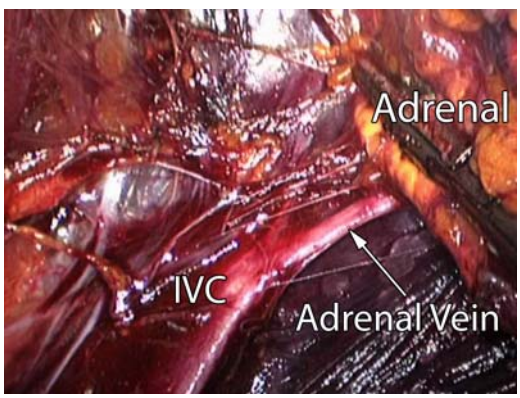

Fig. 34.2. Right adrenal vein anatomy.

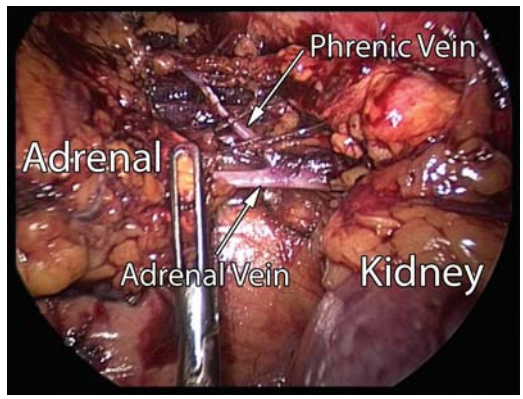

Fig. 34.3. Left adrenal vein anatomy.

Postoperative Care

The postoperative care of the patient is dictated by the pathology of the tumor and is covered elsewhere in this book. The urinary catheter may be removed 4–6 h postoperatively. The patient should be ambulating and eating a regular diet the day of the operation.

Outcomes

As with the laparoscopic lateral transabdominal approach, complications after this operation are not common. In the largest series to date, the incidence of incisional hernia, pneumothorax, and wound infection were all less than 1%. Approximately 8% of patients will experience hypesthesia or abdominal wall laxity. However, these are almost universally temporary findings.

Conclusion

Laparoscopic retroperitoneal adrenalectomy is a safe, fast, and efficient means of resecting the adrenal gland in most patients. The major benefits of this technique over the laparoscopic lateral transabdominal approach include shorter operative times, avoidance of intraabdominal adhesions, and potentially fewer complications. Relative contraindications to this technique include tumor size over 7 cm, body mass index greater than 45, and preexisting increased intraocular or intraorbital pressures. This technique should be part of the armamentarium of endocrine surgeons caring for patients with adrenal disease.

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Section IV
Pancreas

35

Pancreas: Embryology, Anatomy, and Physiology

Tracy-Ann Moo, Rasa Zarnegar and Laurent Brunaud

Embryology of the Pancreas

In the fourth week of embryonic life, the pancreas begins to develop from endodermal structures within the primitive duodenum. The pancreas arises as two separate buds, which subsequently fuse to form a single organ (Fig. 35.1). The dorsal pancreatic bud arises from an evagination of the foregut endoderm and begins to grow into the dorsal mesentery. The ventral pancreatic bud develops from the ventral endoderm of the hepatic diverticulum. Development of the ventral bud occurs by default in endodermal areas where liver induction by fibroblast growth factor (FGF) does not take place. Signaling via activin and FGF originating from the apposing notochord influences the development of the dorsal bud [1]. By the fifth week, the growth of the dorsal bud has surpassed that of the ventral bud. At this time the duodenum begins to rotate, bringing the ventral pancreas along with the common bile duct behind it into contact with the dorsal bud (Fig. 35.2A). By the sixth week, both buds have fused so that the dorsal bud becomes the anterior part of the head, body, and tail of the pancreas, while the ventral bud forms the posterior head and uncinate process (Fig. 35.2B).

After fusion of the two pancreatic buds, the two ducts which have developed within each bud begin to anastomose. Usually, the distal segment of the ventral pancreatic duct extends toward the dorsal duct to form this anastomosis. The duct of the ventral bud then persists as the main pancreatic duct (duct of Wirsung) while the dorsal duct regresses. In up to 60% of the population, the dorsal duct persists as an accessory pancreatic duct (duct of Santorini) [2]. Over the following weeks the main duct elongates into the surrounding mesenchyme giving rise to secondary ducts, which further elongate to form terminal ductules. These terminal ducts are arranged in cell clusters and will form the future pancreatic acini, which performs the exocrine functions of the pancreas. At about week 12, signaling from surrounding mesenchyme promotes the differentiation of the acini. As the acini differentiate they begin to produce low levels of hydrolic enzyme. By birth, these acini will have attained a highly differentiated state, possess an extensive network of protein synthesizing apparatus, and have the ability to store inactive digestive enzymes within cytoplasmic zymogen granules.

The islets of Langerhans, the endocrine component of the pancreas, arise from epithelial cells along the pancreatic acini. These primitive endocrine cells subsequently proliferate into distinct cell clusters and migrate into the mesenchyme of the developing pancreas. In the tenth week angiogenesis begins within the mesenchyme; signals from the developing vasculature cause these cells to develop along an endocrine lineage. Early endocrine cells

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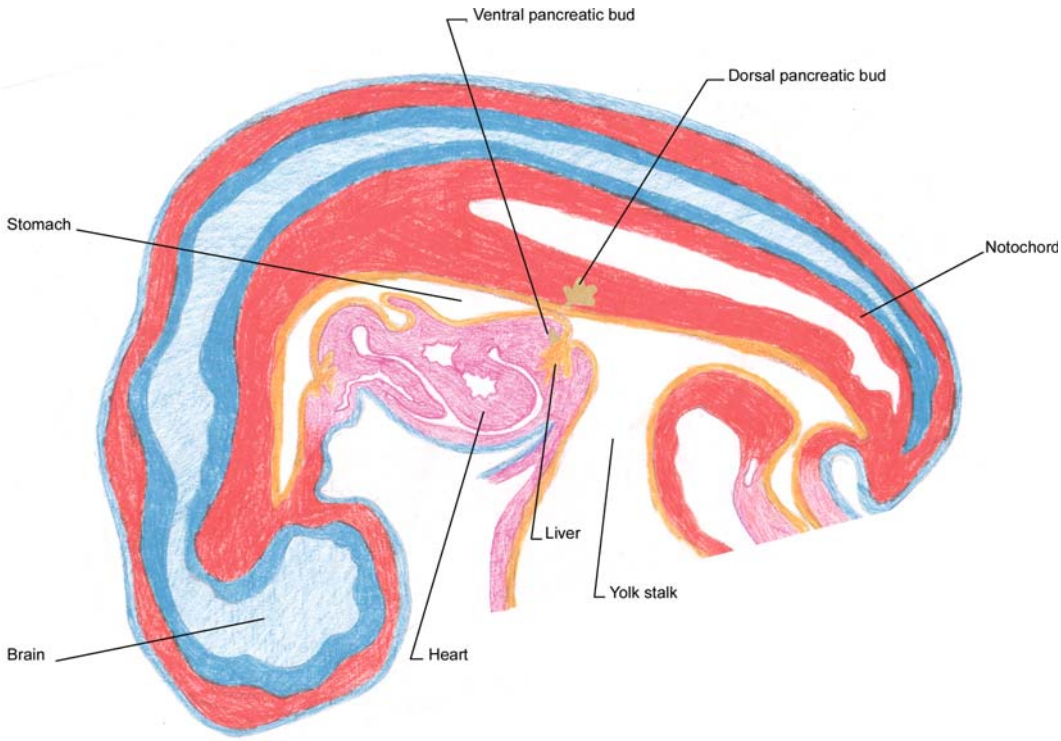

Fig. 35.1. Development of dorsal and ventral pancreatic buds at 4 weeks.

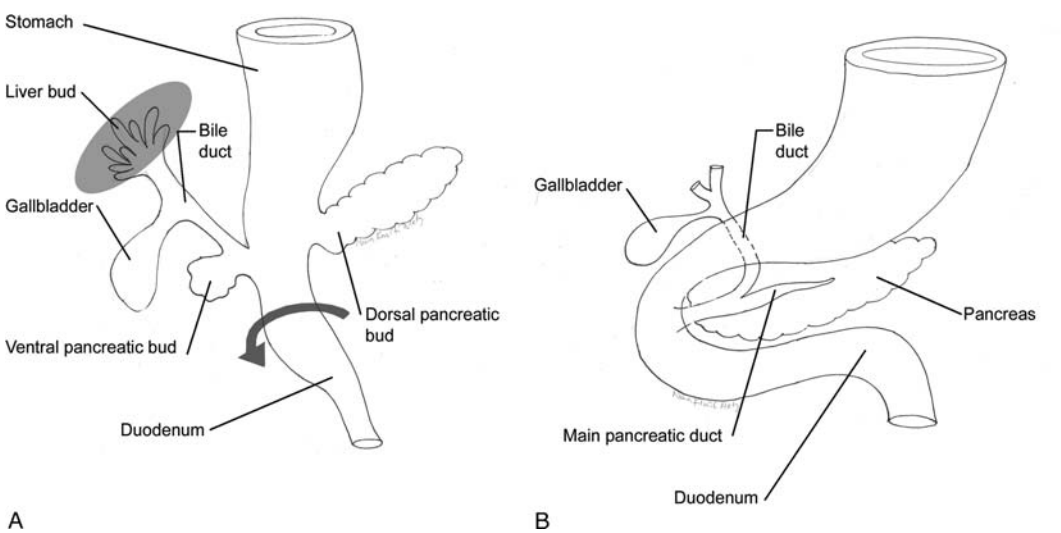

Fig. 35.2. Embryonic development of the pancreas. (**A**) Formation of dorsal and ventral pancreatic buds. (**B**) Fusion of dorsal and ventral pancreatic buds to form a single organ.

differentiate into two types of precursor cells [1]. One precursor cell type differentiates into glucagon producing alpha cells and PP (F cells) cells which produce pancreatic polypeptide. The other precursor cell differentiates into beta and delta cells, which secrete insulin and somatostatin respectively. Beta and delta cells are distributed evenly throughout the pancreas whereas alpha cells are located more in the body and tail. PP cells are mainly located in the posterior head [3].

Developmental Anomalies of the Pancreas

The complex sequence of events that take place during pancreatic development allows for the occurrence of variations as well as anomalies. Errors in the critical steps of rotation and fusion produce an annular pancreas or pancreas divisum. Failure or incomplete anastomosis of the ducts results in multiple variations in major and minor duct anatomy.

Pancreas Divisum is the most common pancreatic anomaly (10%) [4] and is considered more of an anatomic variation. It occurs when the dorsal and ventral pancreatic buds fail to fuse or fuse incompletely. In this instance, the smaller duct of Santorini drains the majority of the pancreas. It was previously hypothesized that pancreas divisum increased the risk of pancreatitis, as a result of a more frequent functional obstruction of the duct of Santorini. This however has not been substantiated by large studies where the incidence of pancreatitis in pancreas divisum was similar to that of the general population [4, 5].

Annular pancreas occurs when a band of normal pancreatic tissue extends from the head of the pancreas and completely encircles the second portion of the duodenum. It has an estimated incidence of 1 per 20,000 and 50% of patients will present with duodenal obstruction at birth or during the first year of life [6]. The exact manner in which an annular pancreas forms is unknown. One theory is that the ring results from hypertrophy of the left portion of the ventral bud, which then grows in opposition to the right portion of the ventral bud. This results in the formation of a constricting ring around the duodenum. It has also been postulated that the ring results from the terminal segment of a single ventral pancreatic bud adhering to and encircling the duodenal wall [7].

Aplasia and hypoplasia: The complete absence of the pancreas is a rare and fatal event [7]. In the absence of insulin, intrauterine growth retardation occurs and symptoms of malabsorption and diabetes mellitus manifest at birth [8]. Hypoplasia, on the other hand, involves a partial agenesis of the pancreas usually involving the dorsal pancreatic bud. Unlike pancreatic aplasia, both endocrine and exocrine functions are typically preserved.

Ectopic pancreas occurs when normally differentiated pancreatic tissue develops outside the pancreas, usually within the gastrointestinal tract. This is typically found incidentally at endoscopy, surgery, or on autopsy. Ectopic tissue is commonly located in the stomach, duodenum, jejunum, or within a Meckel's diverticulum. It occurs less frequently in the ileum, liver, spleen, biliary tract, mesentery, and umbilicus. Ectopic pancreas within the gastrointestinal tract is usually asymptomatic, however may result in ulcerations and GI bleeding [7]. Ectopic pancreatic tissue is thought to arise within the gastrointestinal tract from pluripotent endodermal cells of the foregut.

Anatomy of the Pancreas

The pancreas is a coarsely lobulated, elongated gland located in the retroperitoneum of the upper abdomen. It possesses both endocrine and exocrine functions vital to glucose homeostasis and nutrient digestion. On average the pancreas measures 15–20 cm in length, is about 3 cm wide, and has a thickness of about 1–1.5 cm. In an adult the average weight is 75–100 g. It can be divided into five areas: the head, uncinate process, neck, body, and tail (Fig. 35.3). The head of the pancreas lies within the inner curvature of the duodenum. It is directly anterior to the inferior vena cava and in proximity to the hilum of the right kidney, renal, and gonadal vessels. It is covered anteriorly with peritoneum, with the inflection of the transverse mesocolon passing midway through the head and along the inferior border of the body. The lower portion of the pancreatic head forms the uncinate process, which extends to the left and lies superior to the third portion

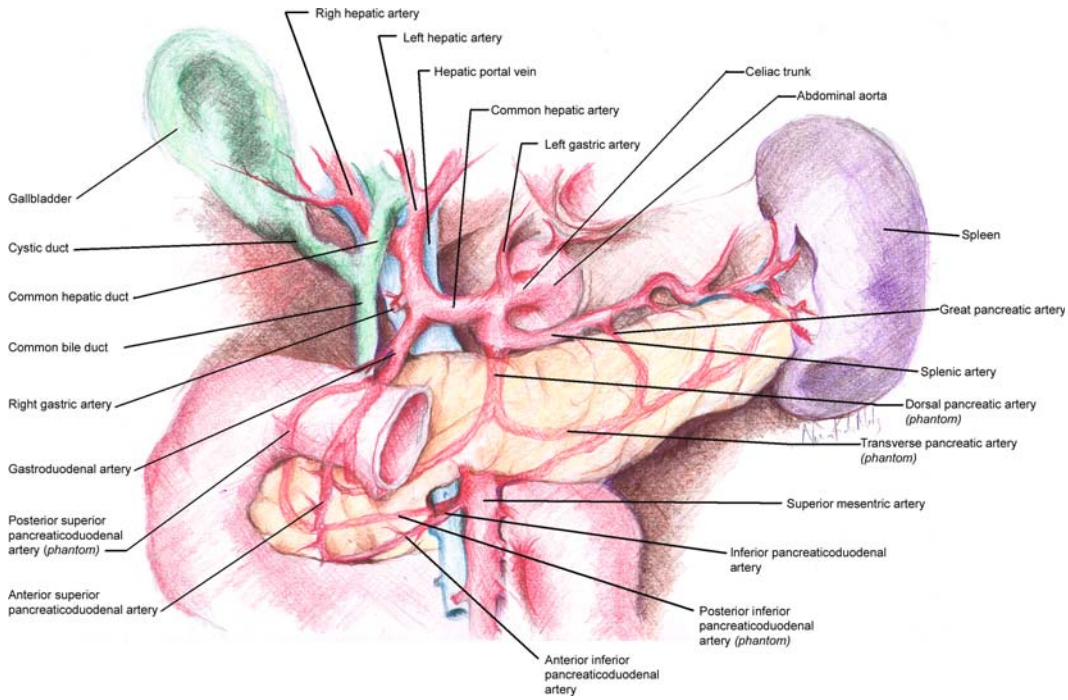

Fig. 35.3. Anatomy of the pancreas.

of the duodenum and posterior to the superior mesenteric vessels. The neck is a 2-cm portion which lies anterior to the formation of the portal vein. It joins the body which runs to the left and slightly upward along the posterior abdominal wall at the level of L1-L2. Posterior to the body is the aorta and the origin of the superior mesenteric artery. Also lying posteriorly are the left kidney, renal vessels, and the left adrenal gland. The body narrows into the relatively mobile tail which terminates at the hilum of the spleen within the splenorenal ligament.

Peritoneal Attachments

The pancreas lies within the lesser sac (omental bursa), covered anteriorly by peritoneum that is continuous with the peritoneal coverings of the posterior stomach and the anterior duodenum. The peritoneal attachment of the transverse mesocolon forms a double layer and usually runs along the inferior border of the body. Posterior to the body the middle colic artery originates from the superior mesenteric artery and runs forward to travel between the layers of the transverse mesocolon. The posterior pancreatic surface has no peritoneal covering. At the tail of the pancreas, the peritoneal reflection forms the splenorenal ligament.

Pancreatic Ducts

The main pancreatic duct (duct of Wirsung) runs axially through the pancreatic parenchyma midway between the superior and the inferior border and closer to the posterior than anterior surface. It begins in the tail and passes through the body, down to the neck, and then to the head where it meets the common bile duct forming the ampulla of Vater. The ampulla of Vater then enters the posteromedial wall of the second part of the duodenum through the major papilla (Fig. 35.4). Within the duodenal wall, surrounding the terminal portion of the ampulla of Vater, is a smooth muscle sphincter complex (Sphincter of Oddi). This sphincter controls exocrine secretions from the common bile duct and main pancreatic duct. In about 14% of patients the common bile duct and main pancreatic duct enter the duodenum through separate orifices.

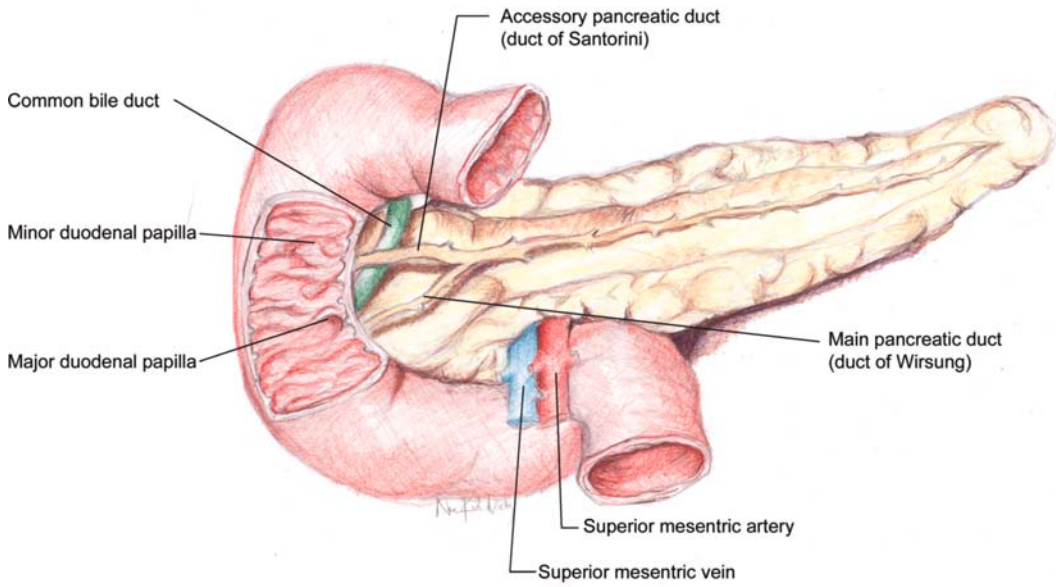

Fig. 35.4. The pancreatic ducts.

The accessory pancreatic duct (duct of Santorini), when present, drains the anterosuperior portion of the head. It enters the duodenum through the minor papilla, which is often located approximately 2 cm superior to the major papilla (Fig. 35.4). The pancreatic duct at its widest point – the entrance to the duodenum – measures 3.1–4.8 mm, within the body it averages 2–3.5 mm and toward the tail it tapers to a diameter of 0.9–2.4 mm [2]. The major pancreatic arterial and venous structures are located posterior to the main pancreatic duct.

Arterial Supply of the Pancreas

The blood supply to the pancreas originates from the celiac trunk and the superior mesenteric artery. The pancreaticoduodenal arcades provide most of the blood supply to the head of the pancreas and the duodenum. The paired superior anterior and posterior pancreaticoduodenal arteries arise from the gastroduodenal artery which is a branch off the common hepatic artery. These arteries descend and coalesce with the inferior anterior and posterior pancreaticoduodenal branches from the superior mesenteric artery to form the pancreaticoduodenal arcades (Fig. 35.3). Both the head of the pancreas and the duodenum share a common blood supply derived from these arcades. The posterior superior pancreaticoduodenal artery also supplies the distal common bile duct and the ampulla of Vater. Occasionally, the inferior pancreaticoduodenal artery arises from the first jejunal branch of the superior mesenteric artery. The uncinate process is supplied by smaller vessels arising either from the inferior pancreaticoduodenal arteries or directly from the superior mesenteric artery.

The splenic artery, as it courses along the superior border of the pancreas, gives off multiple branches supplying the neck and body (Fig. 35.3). The major branch from the splenic artery is the dorsal pancreatic artery which may in some cases arise directly from the celiac (22%), superior mesenteric (14%), or common hepatic artery (12%) [9]. The dorsal pancreatic artery gives off a left and right branch. The right branch usually anastomoses with the posterior superior arcade. The left branch will form the transverse pancreatic artery. This artery runs along the posteroinferior border of the pancreas and anastomoses with the more distal splenic artery branches, the great pancreatic and caudal pancreatic arteries. The great pancreatic artery is the largest splenic artery branch and arises

from the splenic artery between the body and the tail of the gland. The tail is supplied by the caudal pancreatic arteries, which generally arise from the splenic or left gastroepiploic arteries.

There are several notable variations in hepatic artery origin. These variations are relevant to pancreatic surgery, as they are often closely related to the head of the pancreas and at risk of injury during pancreaticoduodenectomy. In most of the population, the hepatic artery branches from the common hepatic artery, which itself derives from the celiac trunk. However, a common hepatic artery may arise directly from the superior mesenteric artery. It sometimes passes through the head of the pancreas and behind the portal vein, before bifurcating into right and left hepatic artery branches. Accidental ligation of this artery will lead to hepatic ischemia. An aberrant right hepatic artery arising from the superior mesenteric artery is also commonly found. This artery may pass posterior to the head before entering the porta hepatis posterior to the common bile duct or portal vein. An anomalous left hepatic artery may arise from the superior mesenteric artery or the gastroduodenal artery [3].

Venous Supply

The pancreatic veins generally run parallel and superficial to the arteries. The head is drained by the pancreaticoduodenal venous arcade. The posterior superior pancreaticoduodenal vein often crosses the bile duct posteriorly to empty into the portal vein at the superior margin of the pancreas. The anterior superior pancreaticoduodenal vein drains into the superior mesenteric vein via the gastrocolic trunk. Both the inferior anterior and the posterior pancreaticoduodenal veins drain into the superior mesenteric vein. At times, they converge before joining the superior mesenteric vein. The splenic vein runs along the posterior superior border of the pancreas receiving tributaries from the tail, body, and neck. It joins the superior mesenteric vein behind the neck of the gland to form the portal vein. The transverse pancreatic vein courses inferior to the splenic vein and empties into the inferior mesenteric vein. The inferior mesenteric vein then empties into either the splenic (60%) or the superior mesenteric vein (40%) [9].

Lymphatic Drainage

The pancreas possesses an extensive network of lymphatics. Within the lobules of the gland, lymphatics are relatively sparse. However lymphatics are substantial within the inter- and intralobular spaces and are associated with blood vessels and connective tissue. These interlobular lymphatics travel with blood vessels to the surface of the gland where they drain to lymph nodes surrounding the pancreas. The superior lymphatic vessels course along the upper border of the pancreas closely associated with the splenic vessels. They receive lymphatic flow from the body and tail and empty into the superior body and splenic lymph nodes. The head of the pancreas is drained by lymphatics, which empty into the anterior and posterior pancreaticoduodenal lymph nodes. Also receiving lymph from the head and body are the gastroduodenal, pyloric, and hepatic nodes. Lymph may also flow directly from the head to the juxta aortic and paraaortic lymph nodes. The tail and the left side of the body empty into the splenic nodes, which adjoin the hilum of the spleen. The gastrosplenic nodes lying within the gastrosplenic ligament receive lymphatic drainage from the tail and the left part of the pancreatic body [10].

Innervation of the Pancreas

The pancreas has both sympathetic and parasympathetic innervation, which regulate pancreatic blood flow as well as endocrine and exocrine function. The pancreas is also richly innervated with pain fibers from the celiac plexus and splanchnic trunks. Parasympathetic innervation originates from the vagus nerve, which transmits preganglionic input from the brainstem. The vagal nerve fibers pass through the celiac ganglion without synapsing; instead they terminate at intrapancreatic ganglion cells which then give off postganglionic fibers to innervate the islet cells, acini, and ducts. Signaling from the vagus is known to stimulate release of insulin and other pancreatic hormones [11].

The sympathetic nerves originate from the splanchnic trunks, which travel to the celiac and superior mesenteric ganglia where they synapse and send postganglionic fibers to

innervate the pancreas. Postganglionic nerve fibers innervate blood vessels as well as endocrine cells [12].

Physiology of the Pancreas

The pancreas plays a key role in glucose homeostasis as well as in the digestive process. These functions can be separated into exocrine and endocrine functions, each possessing unique physiology. In this chapter we focus on the endocrine physiology of the pancreas.

The endocrine pancreas is comprised of islets of Langerhans, which are distributed throughout the pancreas, and makes up approximately 1–2% of its mass. In a normal pancreas there are about 1,000,000 islets of Langerhans. These islets vary in size and may contain several thousand cells of different endocrine type. It was previously thought that human islets are much like the rat islet, where beta cells are concentrated at the core and alpha, delta, and PP cells are scattered throughout the mantle. However, more recent studies on human islets have shown that beta, alpha, and delta cells are generally aligned along blood vessels in no particular order. In fact, beta cells are often found in contact with other nonbeta cells [13]. Beta cells, the insulin-producing endocrine cells of the pancreas, make up 60–80% of islet cells. The glucagon-producing alpha cells make up 20–30% endocrine cells and delta cells around 5–15%. Delta and PP are scattered throughout the islet and secrete somatostatin and pancreatic peptide respectively. Pancreatic islets have an extensive capillary network with at least one arteriole supplying each islet [14]. Scanning electron microscopic studies of rat islet cells indicate that arterial blood enters the islet mantle at one pole and crosses the core to the opposite pole where it then leaves the islet [15]. Physiology studies have also suggested a unidirectional flow of blood with delta cells located downstream from beta cells [16]. A unidirectional flow of blood supports the hypothesis that secretory products of beta cells exert a paracrine effect on the downstream islet cells. However, this requires further anatomic and physiologic investigation.

Beta Cells

Beta cells are the insulin-producing cells of the pancreas. Morphologically these cells are polyhedral and contain large numbers of secretory granules. Their main peptide product is insulin, a 56-amino acid molecule that is arranged into an alpha and beta chain connected by disulfide bridges. Insulin is an anabolic hormone that stimulates the uptake and storage of glucose and amino acids. It is first produced as a propeptide (proinsulin), which is stored within zymogen granules where it is cleaved into C-peptide and insulin. When beta cells are stimulated, both C-peptide and insulin are released into the blood stream via exocytosis. The release of secretory granules is modulated by a number of factors including circulating levels of glucose and amino acids, signaling from the autonomic nervous system, and the incretin hormones glucose-dependent insulinotropic peptide (GIP), and glucagon-like peptide 1 (GLP-1) (Fig. 35.5).

Beta-cell physiology is quiet complex and has been studied extensively. The main insulin secretagogue is glucose; hyperglycemia induces its secretion in a feedback mechanism, which maintains circulating levels within a narrow physiologic range. Glucose acts on the beta cell through a specific glucotransporter (GLUT2) [17]. The GLUT2 transporter is highly efficient and quickly equilibrates intra- and extracellular glucose levels. On entering the cell, glucose is phosphorylated by glucokinase and enters the glycolytic pathway to produce pyruvate. Pyruvate then enters the mitochondria where it is further metabolized in the tricarboxylic acid cycle (TCA) to form NADH and FADH2 [18]. These molecules carry the reducing power required for the activation of the electron transport chain. The change in membrane potential resulting from activation of the electron transport chain powers the oxidative phosphorylation of ADP to ATP. An enhanced ratio of ATP to ADP within the cell then causes the closure of ATP-sensitive K+ channels, which in turn depolarizes the plasma membrane and opens the voltage-dependent L-type Ca^{2+} channels leading to an influx of Ca^{2+} into the cell. This increased cytoplasmic concentration of Ca^{2+} through its action on protein kinase C, protein kinase A, and calmodulin, initiates exocytosis of insulin containing secretory granules. Other peptide hormones such as GLP-1 and GIP interact with receptors on the beta-cell membrane to increase cAMP which also activates protein kinase A. Amino acids interact with a

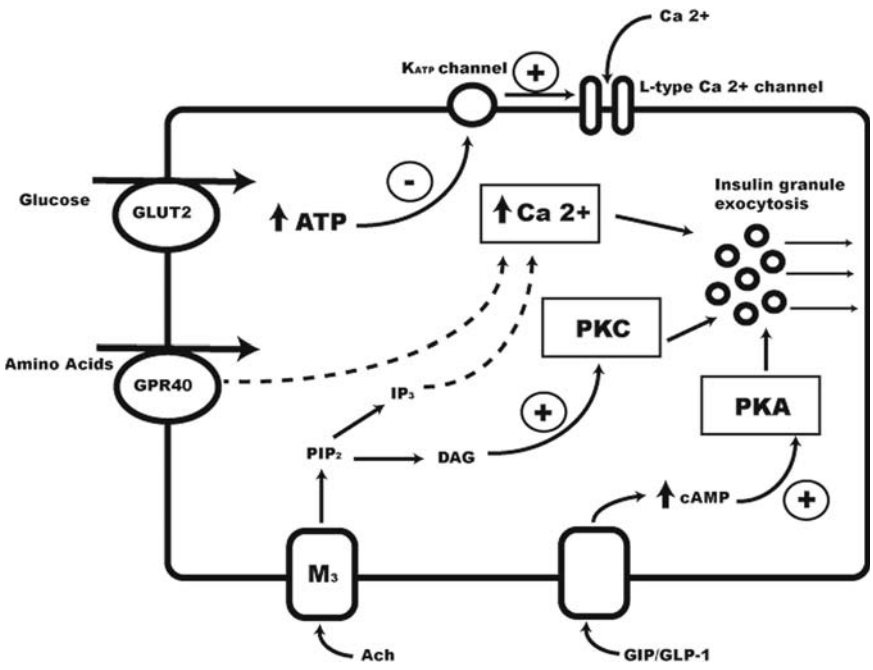

Fig. 35.5. Overview of intracellular pathways involved in insulin secretion. Glucose enters the cell through GLUT2 transporters. The metabolism of glucose increases intracellular ATP which causes the closure of K_{ATP}-channels. Closure of K_{ATP}-channels then leads to membrane depolarization and an influx of Ca^{2+} into the cytoplasm. Increased intracellular Ca^{2+} stimulate the exocytosis of insulin-containing granules. Amino acids bind to the cell membrane receptor GPR40 which acts to directly increase intracellular Ca^{2+} and stimulate granule secretion. Acetylcholine binds to M_3 muscarinic receptors causing the conversion of phosphatidylinositol (PIP_2) to diacylglycerol (DAG) and inositol triphosphate (IP_3). DAG causes insulin secretion by activation of protein activation kinase C (PKC). IP_3 increases intracellular Ca^{2+} which results in granule exocytosis. Glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1(GLP-1) bind to transmembrane receptors which stimulates the production of cyclic AMP (cAMP). cAMP then activates protein kinase A (PKA) which results in granule exocytosis. Courtesy of Harma Turbendian, Weill Cornell Medical College.

transmembrane receptor GPR40 to increase cytoplasmic Ca^{2+} and thereby stimulate granule exocytosis [18, 19]. Like glucose, the metabolism of amino acids promotes the synthesis of ATP and thus increases the ATP/ADP ratio within the cell.

Beta cells also produce islet amyloid polypeptide (IAPP or Amylin), a 37-amino acid peptide that is also stored in secretory granules and co-released with insulin. The Amylin gene IAPP is expressed specifically in the beta cells of the pancreas [20]. The exact function of amylin is unclear; however it is thought to act as an inhibitor of insulin secretion. Studies have shown that in type II diabetes, amylin peptides aggregate to form amylin fibrils, which are thought to be toxic to beta cells. In fact, amyloid deposits are a characteristic pathologic finding in type II diabetes, and a growing body of evidence connects islet amyloid deposition with beta-cell loss and progressive type II diabetes [21]. In humans, the degree of amyloid deposition has been found to correlate with decreased beta-cell mass as well as severity of type II diabetes [22].

Alpha Cells

Alpha cells are columnar shaped islet cells that contain a large number of secretory granules. The primary secretory product is glucagon, a 29-amino acid peptide. Glucagon acts on the liver during hypoglycemic states to stimulate glycogenolysis and gluconeogenesis thus increasing circulating glucose levels. It is believed that like insulin, glucose acts as the primary glucagon secretogogue; hyperglycemia inhibits secretion while hypoglycemia promotes

it. There is however an ongoing debate as to whether alpha cells respond to fluctuations in plasma glucose, possibly signaling through the autonomic nervous system or through the microcirculatory environment of the cell (paracrine effect) created by the secretory products of the other islet cells [23]. It is likely that all these act as stimuli for alpha-cell secretion of glucagon. Recent studies have shown clear relationships between alpha-cell microenvironment and cell regulation. Specifically, the beta-cell products insulin and zinc have been studied. Studies of rat alpha cells have demonstrated the presence of a cell membrane insulin receptor and have also shown that insulin transiently inhibits electrical activity by hyperpolarizing the cell membrane and consequently inhibiting glucagon secretion [24, 25]. Zinc, which is stored in beta cells along with insulin and released in response to high levels of glucose, is also believed to play a role in cell signaling. In rats, zinc has been shown to reversibly inhibit glucose-stimulated glucagon release from alpha cells and also reversibly activate K_{ATP}-channels thereby reducing electrical activity and glucagon secretion [25]. Physiology studies on human alpha cells have yet to substantiate these findings. Glucagon secretion is also closely regulated by the autonomic nervous system. Decreased arterial glucose concentration is detected predominantly in the ventromedial hypothalamus. Evidence suggests that glucose-sensing neurons in the ventromedial hypothalamus function through a mechanism similar to that of the beta cell, where activation of K_{ATP}-channels causes the release of neurotransmitters [23, 26]. This leads to increased sympathetic input to the alpha cells and increased circulating epinephrine levels, both of which result in glucagon secretion [23].

Delta Cells

Delta cells are small dendritic cells, which produce somatostatin, a 14-amino acid peptide, initially produced as prosomatostatin. Prosomatostatin is a 92-amino acid peptide, which is cleaved to yield somatostatin-14 and somatostatin-28. Variations in these two molecular forms of somatostatin are found in different tissue types [27]. Somatostatin-14 is the main pancreatic delta-cell product and is a potent inhibitor of both insulin and glucagon secretion. Somatostatin is released from delta cells in response to hyperglycemia and amino acids [28]. Autonomic input occurs via both parasympathetic and sympathetic branches. Parasympathetic activation will stimulate somatostatin secretion while sympathetic activation is inhibitory.

PP Cells

PP cells (F cells) produce pancreatic polypeptide, a 36-amino acid peptide which is secreted predominately by vagal stimulation [29]. Pancreatic polypeptide inhibits secretion of pancreatic enzymes, bile, and also suppresses insulin secretion. However, its main physiologic function remains unknown.

Autonomic Innervation of Islet Cells

Parasympathetic Innervation

The islets of Langerhans are well innervated by the autonomic nervous system. The parasympathetic branch of the autonomic nervous system is an important regulator of physiologic islet hormone secretion [30]. Parasympathetic fibers originate in neurons with ganglia located within the pancreatic parenchyma. The intrapancreatic ganglia receive neural input from the brainstem via the vagus nerve and also receive input from the enteric nervous system. Activation of the vagus stimulates insulin secretion mainly during the cephalic phase of meal-induced insulin secretion. However, recent studies suggest a larger role for vagally induced postprandial insulin secretion [31]. There are two major mechanisms by which vagal stimulation results in the secretion of insulin from beta cells. First, vagal activity leads to the release of acetylcholine, which binds to muscarinic receptors located on the beta-cell membrane (Fig. 35.5). These muscarinic receptors are coupled with sodium channels within the membrane. Activation of sodium channels leads to an increase in membrane potential, intracellular Ca^{2+} release, and subsequent secretion of insulin. The vagus can also act to stimulate the release of GLP-1 from the intestinal L cells. GLP-1 binds to

specific receptors on the beta-cell membrane, which induces adenyl cyclase and the conversion of ADP to cAMP. Cyclic AMP then activates protein kinase A, which causes an increase in intracellular calcium and the release of insulin. Second, the vagus may act through an acetocholine-mediated increase in phospholipases A2, C, and D which hydrolyzes phosphatidylinositol to diacylglycerol (DAG) and inositol triphosphate. DAG then stimulates protein kinase C which phosphorylates myristoylated alanin-rich protein kinase C and exocytosis of granules [32].

Sympathetic Innervation

The beta cells of the pancreas receive sympathetic input from the hypothalamus via postganglionic fibers from the thoracic and lumbar sympathetic chain. Sympathetic activation causes the release of norepinephrine and epinephrine which activate α_{2a} and α_{2c} adrenoreceptors. These adrenoreceptors act to inhibit adenyl cyclase and lower levels of cAMP which keeps the potassium channels open, the resting membrane potential negative, and thereby reduces insulin secretion [33]. In alpha cells epinephrine stimulates adenyl cyclase activity which increases intracellular Ca^{2+} and results in glucagon secretion [32]. Sympathetic activation has also been shown to inhibit somatostatin secretion [34].

Neuropeptides Involved in Autonomic Regulation of Islet Cells

The neuropeptides vasoactive intestinal polypeptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) modulate parasympathetic input to the islet cells. VIP is a 28-amino acid neuropeptide that is released from parasympathetic nerve terminals within the islets and acts to stimulate beta-cell insulin secretion as well as alpha-cell glucagon release [30]. PACAP is a 38-amino acid neuropeptide that has also been shown to stimulate insulin and glucagon secretion [35]. Both VIP and PACAP bind to G-protein-coupled membrane receptors which mediate an increase in cAMP and intracellular Ca^{2+} levels, thus facilitating exocytosis of insulin-containing vesicles [33, 36].

The neuropeptide galanin is a 29-amino acid neuropeptide, which is widely distributed throughout the central and peripheral nervous system, the gastrointestinal tract, and the pancreas. It is expressed in the sympathetic nerve terminals surrounding the pancreatic islet cells. Although the underlying molecular mechanisms remain unclear, galanin is a potent inhibitor of insulin secretion. There is experimental evidence that galanin acts directly on the beta cell to inhibit adenyl cyclase and decrease cAMP [37]. It has also been shown to inhibit somatostatin secretion and stimulate glucagon secretion.

Neuropeptide Y (NPY) is a 36-amino acid peptide that shares structural homology with pancreatic polypeptide and peptide YY. It is produced in the central and peripheral nervous system. Release of NPY has been demonstrated at sympathetic nerve terminals of islet cells. It is believed that NPY plays a role in the autonomic regulation of insulin secretion. Islet physiology studies have demonstrated an inhibitory effect on insulin release in several species [30]. Further human islet studies are required to substantiate these findings.

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36

Pancreatic Imaging: The Value for Surgery of Neuroendocrine Pancreatic Tumors

Bruno Niederle, Brigitte Happel, Amir Kurtaran, Dermot O'Toole, and Wolfgang Schima

Introduction

As shown recently [1] 10% of all gastrointestinal tumors arising from gastrointestinal neuroendocrine cells diagnosed within 1 year are localized in the pancreas. Therefore pancreatic neuroendocrine (islet cell) tumors (PNET) are rare neoplasms and represent a heterogeneous group of tumors with distinct functional and biological behavior depending on clinical symptoms and tumor size.

In contrast to former views [2] preoperative imaging is of utmost importance and an integral part of the preoperative work up of PNETs in order to plan the surgical procedure adequately.

To date there is no single imaging modality which can reliably show all PNETs. Sensitivity and accuracy depend on the size ($\leq$20 mm/ $>$21 mm), the biological behavior (benign/ malignant; functional/nonfunctional), and the site (pancreas/duodenum) of the lesions. To rule out the possibilities of imaging studies available and to estimate their value for planning surgery, the characteristics of various tumors have to be kept clearly in mind.

Insulinoma are the most common functional PNET. They are in the majority small ($<$20 mm), solitary, well-encapsulated, and benign. Insulinomas are almost exclusively intrapancreatic (99%) [3, 4] and are usually homogeneously distributed within the pancreatic gland.

Gastrinoma are by the majority small ($<$20 mm), often multiple, and may be simultaneously located in the pancreas and the duodenal wall (gastrinoma triangle; this includes the duodenum, the pancreatic head, and the hepatoduodenal ligament) [5]. Gastrinomas tend to occur more frequently in the gastrinoma triangle; however, tumors are also described in other parts of the pancreas and an extrapancreatic localization is frequent, ranging from 30 to 60% of cases (primaries? lymph node metastasis?) [3, 6–9]. The majority of the tumors behave malignant and therefore show lymph node metastases at the time of surgery.

Glucagonoma, vipoma, and somatostatinoma are more than 90% malignant, located in the pancreatic body or tail, and at the time of diagnosis are $\geq$20 mm.

The majority of *nonfunctioning PNETs* are $>$20 mm, are located in the pancreatic head, and are malignant.

Multiple endocrine neoplasia 1 (MEN 1) is associated with multiple functional and nonfunctional PNETs in 40–60% and may be documented in all parts of the pancreas. The most common functioning tumors associated with MEN 1 are gastrinoma (Zollinger–Ellison syndrome, pancreatic or duodenal localization, frequently multiple) and insulinoma. Other very rare tumors include vipoma or glucagonoma.

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Size and Malignancy

"Size" is an easily available, objective, and important parameter used for the current pathohistological classification [10] and for the proposal of a new TNM staging including a grading system [11] of PNETs and may, together with the functional status, help to predict the biological course of the tumor. In the majority of patients, neuroendocrine tumors confined to the pancreas with a size $\leq$20 mm behave "benign," while tumors confined to the pancreas but revealing a size $>$21 mm assimilate an "uncertain" (well-differentiated endocrine tumor) or "malignant potential" (well-differentiated or poorly differentiated endocrine carcinoma). Using cross-sectional imaging modalities these neuroendocrine carcinomas are usually large tumors showing invasion of adjacent organs, enlarged lymph nodes, and metastasis to the liver [12].

A variety of preoperative (conventional and functioning) imaging modalities for the detection of these tumors is currently available. Their combined application seems mandatory to improve the preoperative evaluation of PNETs, localizing small functioning and nonfunctioning tumors, differentiating PNETS from pancreatic adenocarcinoma, identifying signs of malignancy, and evaluating metastatic disease.

This chapter focuses on all imaging methods, discusses their diagnostic potential and limitations, and describes a rational approach of how to optimize the use of imaging PNETs preoperatively to be of value for the endocrine surgeon.

Radiological Imaging Techniques

Transabdominal Ultrasonography

Transabdominal ultrasound (US) provides a useful tool for the preliminary investigation of islet tumors of the pancreas. US imaging does not require ionizing radiation, is widely available, noninvasive, and relatively cheap. However, this imaging modality is an extremely operator-dependent procedure and needs the hand of an experienced sonographer. The principal difficulties in detecting PNETs with US arise because of the anatomy (see Chapter 35) of the organ and the small size of the tumors at the time of presentation. Obesity, previous surgery, and overlying bowel gas provide further obstacles to adequate pancreatic imaging.

Initial scanning is performed with the patient supine and in lateral decubitus position, using a 3.5- to 5-MHz probe. Ideally the patient should fast for at least 6–8 h to reduce acoustic shadowing of the stomach, which obscures the pancreas body and tail during US. Accordingly, wide variations in sensitivity rates of US can be found in the literature. The reported detection rates vary between 23 and 79% [13–18].

The small islet tumors are usually well defined and round or oval in shape, and although they generally appear hypoechoic in relation to normal pancreatic tissue, they may have a hyperechoic capsule. The nonfunctioning PNETs are easier to detect because they reach a larger size before causing symptoms. Larger tumors may be moderately echogenic, heterogeneous, and may contain fluid-filled areas or cystic changes or calcifications. In addition to its role in localizing the primary tumor, US can be used to search for metastases in the liver and regional lymph nodes. Moreover, newer US techniques such as US contrast agents may further improve the diagnostic yield of transabdominal US. However, transabdominal US alone is not sufficient for localization of PNETs and staging of the disease (Table 36.1).

Endoscopic US

Endoscopic US (EUS; also known as endosonography or echoendoscopy) plays a pivotal role in PNET assessment especially in patients with small and difficult-to-locate primaries or in the ever-increasing cases of incidental findings of nonfunctional PNETs. A multicenter study verified the ability of EUS to localize pancreatic PNETs in patients where transabdominal US and CT were negative [8]. Whether these results remain true in the era of modern multidetector CT (MDCT) remains to be proven. However, at least in small pancreatic cancers the superior sensitivity and excellent negative predictive value of EUS compared with MDCT has been shown [19].

Table 36.1. Localization of pancreatic neuroendocrine tumors: sensitivity of transabdominal ultrasound, computed tomography, various types of angiography, and endoscopic ultrasound

			Trans-abdominal ultrasound	Computed tomography		Selective angiography	Arterial stimulation and venous sampling	Endoscopic ultrasound
Author [ref]	Year	Tumor type	Sensitivity % (*n*)	Technique	Sensitivity % (*n*)	Sensitivity % (*n*)	Sensitivity % (*n*)	Sensitivity % (*n*)
Galiber [15]	1988	Insulinoma	61 (28)	Incremental	30 (23)	54 (26)	–	–
Rothmund [18]	1990	Insulinoma	39 (142)	NA	33 (246)	62 (305)	–	–
Böttger [93]	1990	Insulinoma	70 (21)	Incremental	73 (15)	67 (30)	–	–
Rosch [8]	1992	All NETs	–	–	–	–	–	82 (37)
Aspestrand [94]	1993	All NETs	–	Incremental	79 (29)	72 (29)	–	–
Angeli [13]	1997	Insulinoma	79 (28)	NA	45 (28)	69 (28)	–	–
Kuzin [16]	1998	Insulinoma	30 (78)	NA	24 (38)	56 (118)	90 (17)	–
Xi Chen [14]	2002	Insulinoma	30 (30)	NA	63 (41)	27 (11)	90 (10)	33 (9)
Kirchhoff [65]	2003	Insulinoma	8 (13)	Helical	46 (13)	69 (13)	92 (13)	–
Gouya [95]	2003	Insulinoma	–	Multidetector				
				Thin slice	94 (15)	–	–	94 (30)
				Thick slice	57 (8)	–	–	
Wiesli [67]	2004	Insulinoma	–	Helical	59 (27)	–	96 (27)	–
Queiroz [17]	2006	Insulinoma	23 (64)	NA	28 (64)	38 (64)	67 (64)	75 (64)
Wong [96]	2007	Insulinoma	–	NA	31 (13)	46 (6)	40 (14)	–

Note: NA: not available; NET: neuroendocrine tumor.

Newer methods such as EUS-contrast studies and elastography [20, 21] may enhance EUS performance in this field. While the performance of EUS in preoperative localization of the primary appears unquestionable (detection of loco-regional extension is also possible), it cannot remain the sole examination in tumor stage classification and should be combined with classical axial imaging and especially somatostatin (SST) receptor scintigraphy (SRS) in a multidisciplinary fashion.

Tumor Characteristics at EUS

PNETs are generally hypervascular and well limited. Typically the EUS pattern is a hypoechoic, homogeneous lesion with distinct margins with peripheral rim enhancement (Fig. 36.1A). Theses tumors present less frequently with a hyperechoic or isoechoic texture, and in such circumstances distinguishing them from adjacent parenchyma may be challenging. Cystic PETs also exist although are in fact rare and tend to be nonfunctional [22]. Other features are the presence of calcifications and zones of necrosis, the latter more usually occurring in large nonfunctional tumors. The size and intrapancreatic distribution varies according to tumor type.

The approach to examining the pancreas has been described elsewhere in detail [23], but a structured appraisal of the pancreatic head followed by the body and tail (the latter may require patient repositioning) should be ensured. Upon tumor detection, a detailed examination of the lesion includes exact localization

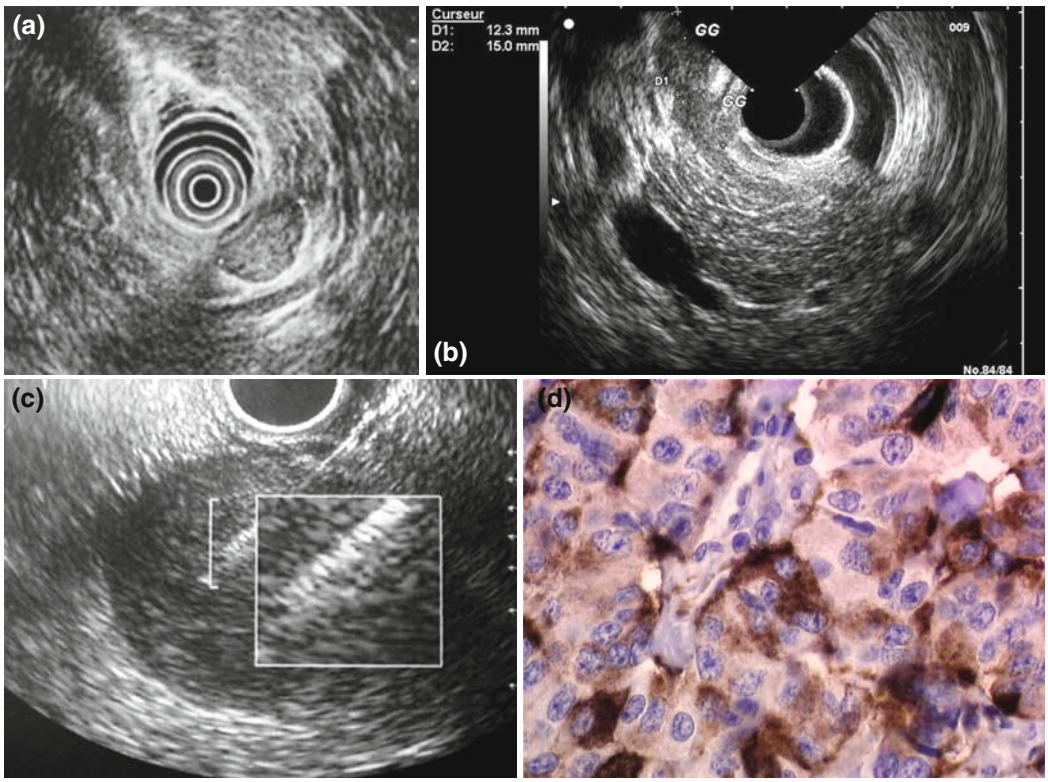

Fig. 36.1. (**A**) Nonfunctional PNET situated in the pancreatic body using EUS (7.5 MHz frequency). (**B**) Two peri-duodenal lymph nodes (GG) measuring 12.3 and 15 mm in diameter are clearly seen at EUS in a patient with a Zollinger–Ellison syndrome. (**C**) Biopsy (EUS-FNAB) under EUS guidance with a small 22 G needle (*white line* and *box magnification*) positioned in the centre of a well-defined homogeneous hypoechoic PNET in the pancreatic body. (**D**) Subsequent histology with immunohistochemistry showed a well-differentiated tumor staining positively for chromogranin A (*brown* staining).

according to surgical anatomical landmarks; the precise relation between the tumor and the main pancreatic duct and other adjacent structures should also be assessed due to the possibility of performing limited pancreatic resection and notable enucleation. The possibility of multiple tumors as in patients with MEN 1 requires a careful methodological approach. Finally, separate analysis of all lymph node stations should be performed: peri-pancreatic, mesenteric, hepatic hilum, pyloric, peri-gastric, and coeliac (Fig. 36.1B). In cases of gastrinomas, the duodenal wall – from the duodenal bulb to the third portion of the duodenum – should carefully be examined [9, 23] in a final step using a high-frequency transducer (at least 12 MHz) in order to detect small tumors.

Performance of EUS in Different Tumor Types

Noninvasive techniques yield preoperative detection rates for small (<1 cm) *insulinomas* of between 40 and 60% [24–26]. Invasive methods, while relatively sensitive [27–29] (60–80% detection rates), have been rendered obsolete by the performance of preoperative EUS, which in addition is less dangerous with lower morbidity. The characteristics at EUS of insulinomas were recently reported by Anderson et al. in 36 tumors [30]. The majority were hypoechoic (78%) and homogeneous (89%) and less-frequently isoechoic (19%) or hyperechoic (3%) [30]. The overall sensitivity of EUS in the preoperative localization of insulinomas is excellent (on the order of 80–90% [8, 30–36]). The accuracy of EUS is higher than other imaging techniques including spiral computed tomography (CT), magnetic resonance imaging (MRI), and SRS (Tables 36.1 and 36.3). While SRS is highly sensitive for most other PNETs, lack of the SST receptor, sst_2 subtype in 50% of patients with insulinomas explains the low performance in this setting [37, 38]. Another factor influencing the results of conventional imaging (CT, MRI, and SRS) stems from the small size of these tumors [3]. EUS is therefore the preoperative reference examination in cases of suspicion of insulinoma and should be combined with perioperative detection methods (US and palpation). EUS also allows the precise localization of the tumor within the pancreatic parenchyma and will help decide whether the tumor is amenable to a limited resection technique.

As for insulinomas, invasive techniques have become almost obsolete in *gastrinomas* and do not allow for accurate distinction between a duodenal and pancreatic origin [23, 39]. Few prospective studies are available examining the performance of EUS compared with other imaging methods. In addition, interpretation of results is often difficult due to the lack of information concerning a duodenal localization and the absence of a confirmed anatomical site in certain reports [8, 31, 33, 40]. Gastrinomas are almost exclusively hypoechoic and homogeneous (97 and 97%, respectively) [30]. The overall performance of EUS in preoperative detection of gastrinomas is poor compared with other PNETs, and this can be explained by the large proportion of tumors localized within the duodenum [30, 41]. Duodenal gastrinomas are almost always very small and detection even by expert endosonographers rarely exceeds 50% [41]. Results in patients with Zollinger–Ellison syndrome have improved over the years – sensitivity passing from 33 to 54% for duodenal localization over a 10-year period in one recent report; corresponding figures for the detection of intrapancreatic gastrinomas are 75 and 100% over the same period. Indeed, a normal pancreatic EUS in this setting is a strong argument in favor of a primary duodenal tumor. EUS should therefore always be combined with other techniques (at least spiral CT and SRS) to improve results. Combinations of EUS with SRS have yielded detection rates of approximately 90% [35, 41]. The detection of small duodenal localizations may be enhanced using standard axial video endoscopy and intraoperative duodenal transillumination. Finally, careful appraisal for lymph node involvement should be performed as peritumoral lymphadenopathy is frequent in patients with gastrinoma and their identification is possible using EUS in about half of patients [32, 42].

Several groups have underlined the impact of EUS in the accurate detection of sporadic GEP. An interesting application of EUS is the screening and surveillance of MEN 1 patients as has recently been described [43, 44]. These small and multiple tumors render their detection difficult using standard imaging techniques. As shown recently [45] EUS is a more sensitive

technique for the detection and localization of potentially malignant lesions in patients with MEN 1 than CT or transabdominal US. In a prospective study Kann [43] and coworkers were able to show that PNETs are usually slow-growing tumors with a very low risk to metastasize if smaller than 15 mm. Thus surveillance with EUS could help planning the time for surgical intervention. Despite the fact that EUS is an invasive examination method and sedation of the patient is often necessary, complications such as bowel perforation or aspiration in diagnostic procedures are extremely rare and make EUS a fairly safe method [46]. The incidental detection of multiple PNETs should strongly evoke the possibility of MEN 1 and should prompt adequate genetic screening. Screening for PNETs, which have a high incidence in MEN 1 (estimated recently to be approximately 53% [40]), is currently recommended as their presence carries significant impact on survival in these patients [47, 48]. In addition, use of accurate imaging procedures is mandatory because of the lack of a clear genotype/phenotype correlation. Imaging methods with adequate resolution are required in following patients with MEN 1 without or with PNETs $\leq$10 mm. Furthermore, the incidence of nonfunctioning tumors is increasingly recognized in MEN 1 populations (40–50%) [49], and screening in such patients is even more challenging. A recent retrospective study in asymptomatic individuals who were MEN 1 carriers revealed that EUS detected a PET in 14 of 15 cases (93%); 12 had multiple tumors [50] and this led to surgery in 13 patients [50]. The French endocrine tumor study group (Groupe de Tumeur Endocrine) recently reported their prospective experience using EUS in the screening of asymptomatic MEN 1 individuals [49]. This large series of 51 patients found a 55% detection rate of PNETs; more than a third were $>$10 mm at initial screening and 14% were $>$21 mm (the cutoff used by this group for surgery was 20 mm). Follow-up was available for a limited number of patients but EUS appeared to be useful in detecting tumor modifications [49].

The performance of EUS in the detection of *other functional PNETs* [51] is difficult to appreciate owing to their rarity. However, following recent consensus guidelines [51], its use does not appear to be of primary importance as these tumors are frequently large and often presenting at the metastatic stage, and diagnosis is made using standard imaging and SRS in specific clinical circumstances.

Biopsy Using EUS

Biopsy using EUS Fine needle aspiration biopsy(FNAB) (Fig. 36.1C) may be useful in cases of locally advanced disease to confirm the diagnosis [52, 53]. Although the diagnosis in the majority of cases of functional PNET is easy (typical symptoms coupled to standard axial imaging and SRS), it is occasionally necessary to perform a biopsy establishing the diagnosis in rare situations. In reality, when a pancreatic mass presents with characteristic features of an endocrine tumor and appears resectable, no biopsy is indeed required. EUS–FNAB is usually required in doubtful diagnostic cases or prior to surgery in patients where pancreatic resection may carry significant risk (e.g., elderly patients with a probable PNET on standard imaging and diagnostic EUS but with negative SRS). A cytohistological diagnosis may thus be preferable using EUS–FNAB. EUS–FNAB carries several advantages over transabdominal US- or CT-guided biopsy of pancreatic masses, such as proximity to the lesion and the possibility of directing the needle into the target lesion, even for small lesions, under direct US control. Excellent performance in biopsy of pancreatic lesions has been established in many series [52, 54], while remaining a safe technique. Feasibility varies from 90 to 98% and sampling yields adequate tissue, on intention-to-biopsy, in 80–95% of cases. While the diagnostic accuracy of EUS–FNAB is around 90% for pancreatic adenocarcinoma [52, 53], figures are lower for PETs, with figures ranging from 47 to 71% [52, 54, 55]. This appears to be due to the hemorrhagic character of endocrine tumors, which increases the rate of false-negative biopsies [52]. Nonetheless, in about three fourths of patients EUS–FNAB yields a tiny tissue core biopsy where standard histology coupled to immunohistochemistry can be performed (Fig. 36.1D). Finally, the complication rate of EUS–FNAB is low (between 2 and 5%) and in most cases minor [56].

Intraoperative US

Intraoperative US (IOUS) is a useful technique to make the palpating finger of the surgeon to

"see" inside the pancreas. With the lack of gas and obesity, with high-frequency scanners, and with often preoperatively acquired data the sensitivity of IOUS is very high, given a good exposition of the pancreas (down to the uncinate process and up to the very end of the tail) to the sonographic transducer. In combination with palpation, sensitivity has been reported to be between 84 and 100% [15, 57]. The sensitivity for detection of individual masses in patients with multiple tiny PNETs remains still a challenge. These patients almost always have MEN 1, which is apparent preoperatively.

The sonographic appearance of islet cell tumors at IOUS is identical to that of transabdominal US. Lesions are localized as hypoechogenic circular mass well defined from the normal pancreatic tissue. An additional value of high-frequency IOUS is its ability to depict the precise relationship of PNETs to the pancreatic duct and the common bile duct, if tumor enucleation is planned. However, with state-of-the-art preoperative imaging including multiphasic MDCT and EUS an IOUS examination of the gland to look for multifocal tumors is no longer routinely necessary.

Intraoperative Endoscopic US

The use of minimally invasive surgery has been expanding to the resection of PNETs; however, intraoperative localization is the key to successful endoscopic surgery. As shown recently [58] the prospectively use of intraoperative endoscopic US (IOEUS) identified 86% of the tumors. In addition the US provides valuable information regarding the tumors' relationship to the duct and nearby vascular structures, guiding laparoscopic surgery [58, 59–61].

Computed Tomography

New developments in CT technology have resulted in dramatic improvements of CT imaging of the pancreas in the last few years. Modern multidetector (or "multislice") CT (MDCT) scanners produce axial images of very high resolution, providing the surgeon with essential information concerning tumor localization and extent of disease. Compared with transabdominal or endoscopic US and MRI, MDCT appears to have several advantages. It is a fast, robust, and highly standardized method, which provides good results in the vast majority of patients. Compared with endoscopic US, it is rather noninvasive, and not only the pancreas, but also the liver can be evaluated.

Another advantage of MDCT is the possibility of doing the complete staging all at once, as surrounding lymph nodes, infiltration of the environment, as well as distant metastases (e.g., liver metastases) can be visualized during the multiphase CT examination [62]. PNETs are mostly hypervascular and many of them "light up" only for a very short period of time after IV contrast material administration. Thus, a dynamic MDCT examination is the preferred scanning protocol comprising at least three phases. Each scan with a modern MDCT scanner does not take more than 4–5 s, which is important to catch the transient contrast material blush of NET. As a "negative" oral contrast agent, 1,000 ml water just before the examination may help to distend the duodenum (so-called hydro-CT). This advances the diagnosis of the pancreatico-duodenal tumors in or just outside the duodenal wall and delineates the head of the pancreas.

Performance of CT in Different Tumor Types

Insulinomas are usually isodense to normal pancreatic tissue without IV contrast material and are not seen unless there is a contour distortion. Rarely insulinomas may be hyperattenuating on precontrast images due to the presence of calcification. Typically insulinomas are hypervascular and demonstrate a greater degree of enhancement than the normal pancreatic parenchyma during the arterial phase (Fig. 36.2). Many of these tumors are small at diagnosis and are therefore noncontour deforming, so it is important to perceive the vascular blush for the diagnosis. Atypical MDCT appearances of insulinomas include hypovascular and hypoattenuating lesions postcontrast, and cystic or calcified masses precontrast.

Recently encouraging results of MDCT study have been published, which reported correct localization of more than 80% of *gastrinomas* with MDCT (Fig. 36.3) [63]. However, diagnosis of duodenal (extrapancreatic) localization has always been one of the weaknesses of CT

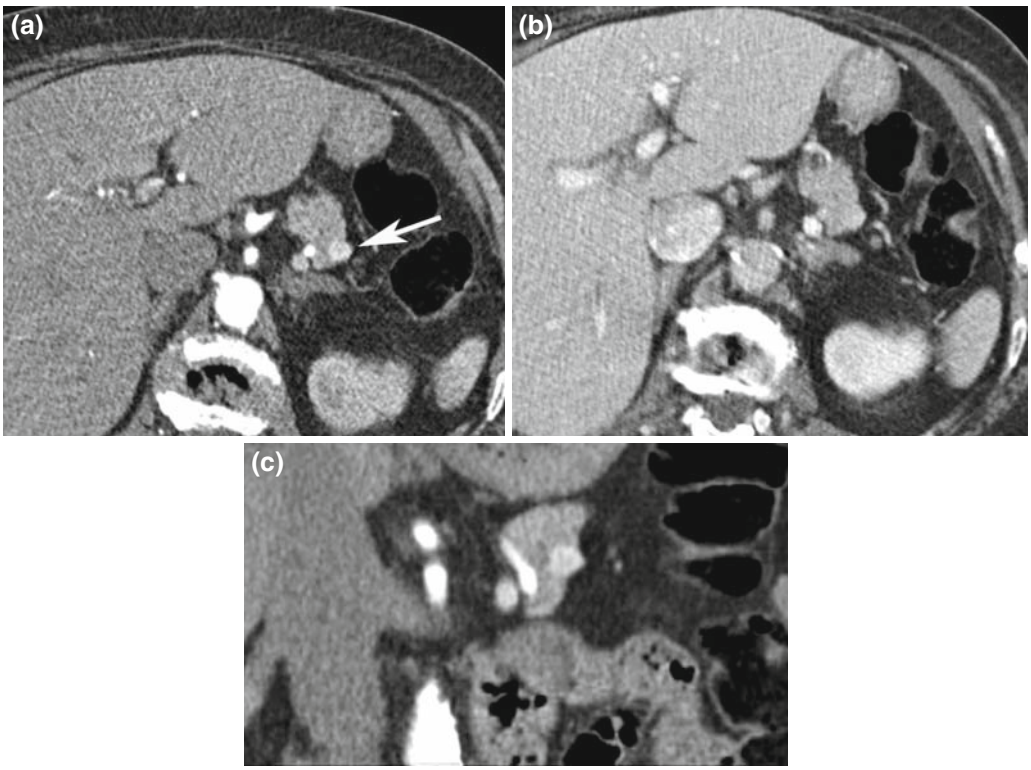

Fig. 36.2. (**A**) Insulinoma of the pancreatic tail. Axial contrast-enhanced MDCT scan obtained in the arterial phase shows a hyperattenuating lesion in the tail of the pancreas. (**B**) In the portal-venous phase the lesion is only barely visible. (**C**): 3D reconstruction of the CT data set in the coronal plane (arterial phase) in the same patient depicts the small hypervascular insulinoma to be very superficial in location.

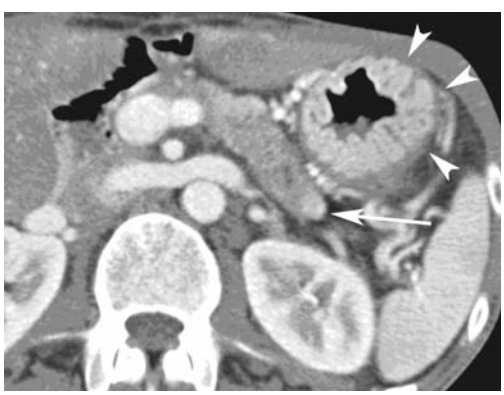

Fig. 36.3. Axial arterial-phase MDCT shows a small slightly hyperdense gastrinoma in the pancreatic tail (*arrow*). Elevated serum gastrin leads to marked thickening of gastric folds (*arrow heads*).

imaging. Because a high proportion of gastrinomas are malignant, metastases may already be present at the time of diagnosis. In this case, localization of the primary tumor becomes less important because there will be palliative therapy instead of surgical cure. *The other functioning tumors* of the pancreas (vipoma: Fig. 36.4; glucagonoma: Fig. 36.5) are even rarer. They tend to reach a greater size and the majority have metastasized by the time of presentation (Fig. 36.6A).

Most *malignant PNETs* demonstrate enhancement characteristics similar to functional tumors. They tend to present as well-defined masses of large size with moderate or strong enhancement after intravenous injection of contrast medium. Other large tumors may be centrally hypoattenuating at the arterial and portal-venous phases due to necrosis (Fig. 36.5). Imaging findings that are useful in the differentiation of endocrine tumors from ductal adenocarcinomas include the presence of calcifications, lack of vascular

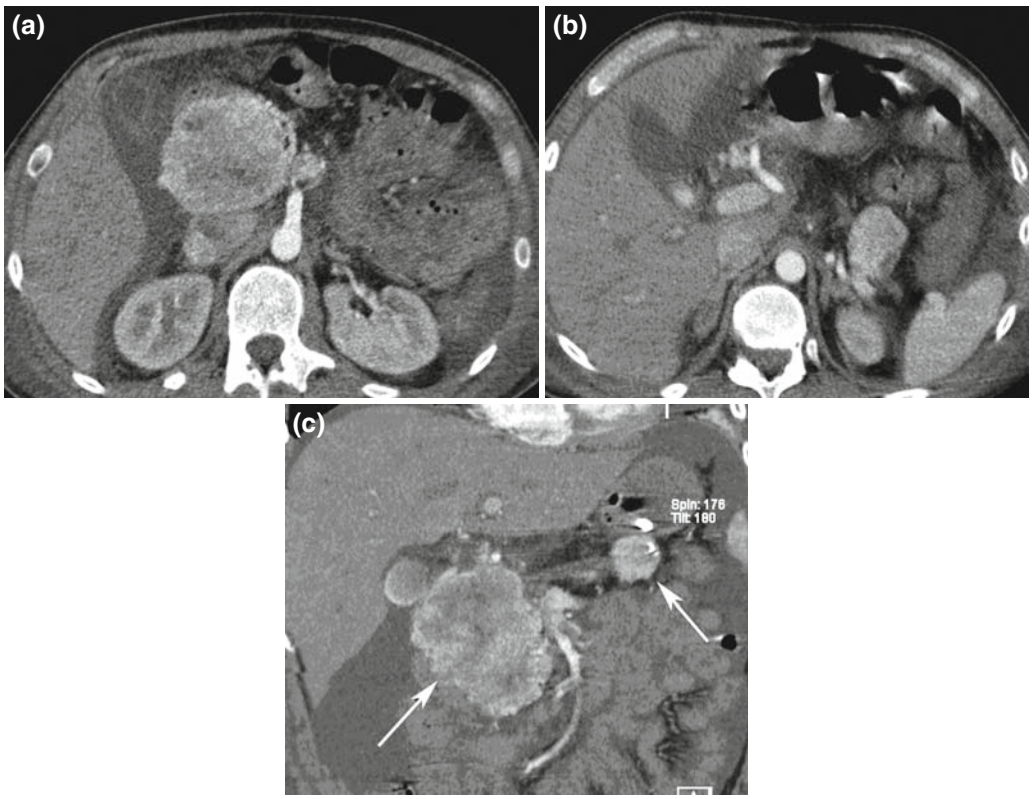

Fig. 36.4. (**A**) MEN 1 – Axial MDCT (arterial phase) demonstrates a large hypervascular tumor of the pancreatic head with areas of necrosis (VIPoma). (**B**) A second VIPoma is detected in the pancreatic tail. (**C**): Curved planar 3D reconstruction along the pancreatic axis shows both tumors in one image.

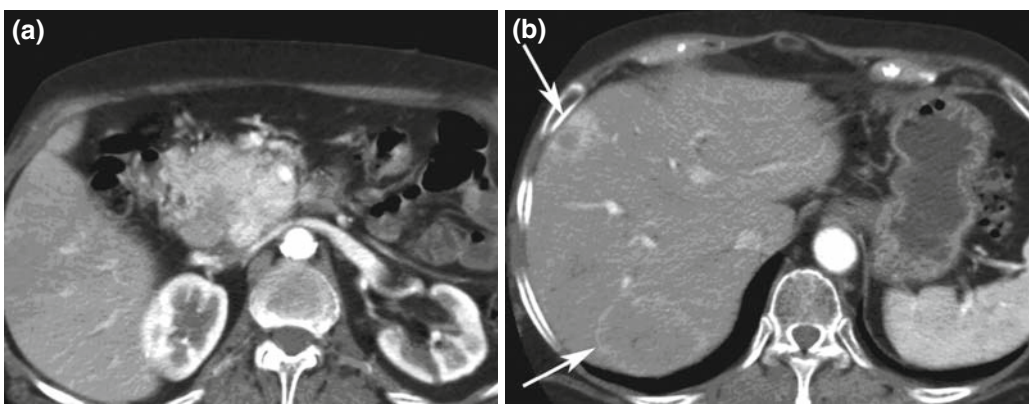

Fig. 36.5. (**A**) Axial arterial phase of a MDCT, showing a large irregular demarcated glucagonoma of the pancreatic head with tumor surrounding of the superior mesenteric artery. (**B**) Axial MDCT image of the liver shows several liver metastases with hypervascular periphery and central necrosis in the arterial phase.

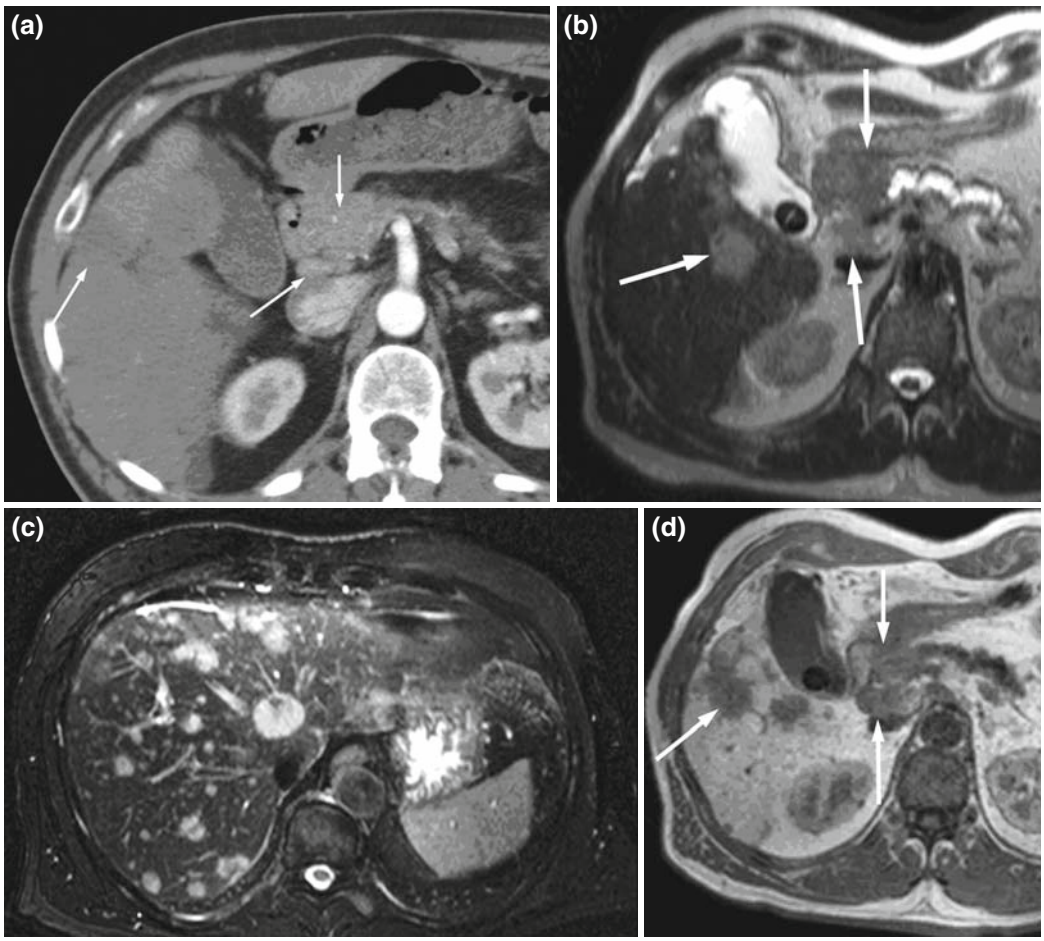

Fig. 36.6. (**A**) Axial arterial phase of a MDCT with an NET of the pancreatic head, metastases of the liver, and lymph nodes (*arrows*). (**B**) Same patient with a T2-weighted TSE fatsat MRI shows the pancreatic tumor with dilatation of the pancreatic duct. Liver and lymph node metastases are seen (*arrows*). (**C**) Axial T2-weighted fatsat MR image, showing multiple liver metastases. (**D**) Axial Teslascan-enhanced MR image, depicting the NET oft the pancreatic head, liver, and lymph node metastases.

encasement, absence of ductal obstruction, less common central necrosis and cystic degeneration, and lack of desmoplastic reaction.

One of the main advantages of MDCT technology is the possibility to produce multiplanar and curved planar reconstructions (MPR, CPR), which can be helpful in demonstrating the tongue-shaped pancreas. MPRs are 2D reformatted images that are reconstructed secondarily in arbitrary planes from the stack of axial image data. Oblique or curved reformations are constructed in an analogous fashion. The MPRs are able to show the topographic relationship between tumor and gland including the pancreatic duct. Thus, they are a helpful tool in deciding whether enucleation is possible or resection of the tumor together with gland has to be performed (Figs. 36.2C, 36.4C, and 36.7C).

Multiphasic helical CT with high-resolution thin sections during the arterial phase provides an accurate and sensitive method for the depiction of islet cell tumors. Previously published studies (Tables 36.1 and 36.2) have reported MRI to be better than helical CT in revealing small PNETs. But with the new developments in multidetector CT technology a multiphasic MDCT examination should be the basic diagnostic tool when a tumor is suspected.

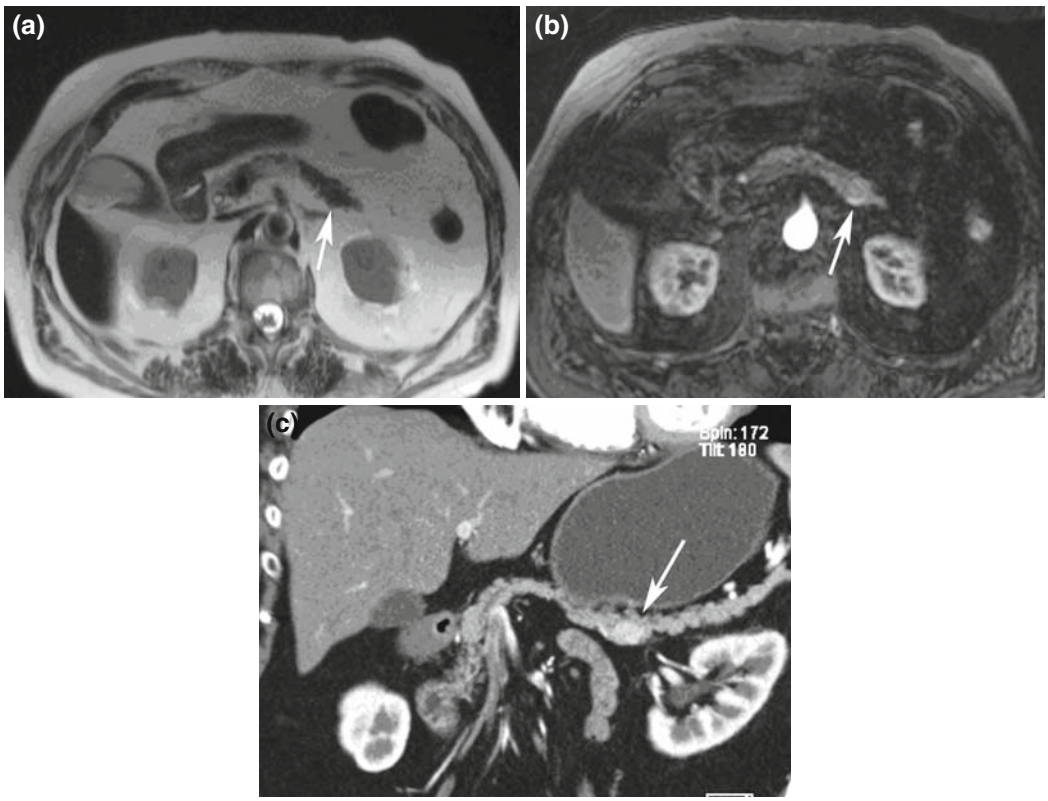

Fig. 36.7. (**A**) Axial T2-weighted MRI image shows a contour deformation of the posterior surface of the pancreatic tail. The insulinoma is isointense to the surrounding pancreas parenchyma. (**B**) Arterial-phase gadolinium-enhanced T1-weighted MRI image shows the hypervascular insulinoma, slightly better demarcated from normal tissue. (**C**) Same patient, curved planar 3D reconstruction of an arterial phase-enhanced MDCT, which is superior to MRI in this case.

Magnetic Resonance Imaging

A central question of several studies has been whether or not MRI is superior to CT in detection of islet tumors of the endocrine pancreas (Table 36.2). The costs for MRI are higher than for MDCT, and the availability of MRI scanners is lower compared with MDCT. Therefore MRI is mostly used if results of the CT examination are inconclusive or in cases of patients being allergic to iodinated contrast agents. Advances of MRI over CT include greater tissue contrast resolution, the absence of ionizing radiation, and the lower incidence of side effects of gadolinium–chelate contrast material administration.

The principle of MRI is based on the inherent motion of hydrogen ion protons within the tissue of the body. Each hydrogen ion has a small magnetic field associated with it which, when exposed to the magnetic field of the MRI, spins or processes at a different rate [64]. The two relaxation times are T1 and T2. T2-weighted images are important in identifying abnormalities. T1-weighted images are useful for depiction of anatomical detail and, together with the gradient-recalled echo imaging, are the sequence used after administration of an MR contrast agent. The most commonly used MRI contrast agent is gadolinium, which is metabolized and excreted in much the same way as iodinated contrast material (in CT), but has a much higher safety profile. Gadolinium is an extracellular paramagnetic agent; the extracellular space consists of the sum of the intravascular and interstitial spaces. This agent has been described as "nonspecific," whereas mangafodipir trisodium (Teslascan®, GE Healthcare, Oslo, Norway) is a specific agent,

Table 36.2. Localization of pancreatic neuroendocrine tumors: sensitivity of computed tomography (CT) and magnetic resonance imaging (MRI)

			CT	CT	MRI	
Author [ref]	Year	Tumor type	Technique	Sensitivity % (*n*)	Field Strength	Sensitivity % (*n*)
Semelka [97]	1993	All NETs	Incremental	65 (10)	–	–
Aspestrand [94]	1993	All NETs	Incremental	79 (29)	1.5 T	100 (10)
Van Hoe [98]	1995	Insulinoma, gastrinoma	Helical	82 (10)	1.5 T	88 (10)
King [99]	1998	Insulinoma	Helical	86 (7)	–	–
Thoeni [100]	2000	Insulinoma, gastrinoma	–	–	1.5 T	<2 cm tumor size
		All NETs				85 (20)
Ichikawa [101]	2000	Nonfunctioning NETs	Helical	69–73 (19)	1.5 T	74–79 (19)
		NETs				
Procacci [102]	2001		Helical	67 (21)	–	–
		All NETs				
Rappeport [63]	2006		Multidetect	83 (19)	–	–
		Insulinoma				
Wong [96]	2007		NA	31 (13)	NA	50 (2)

Note: NA: not available; NET: neuroendocrine tumor.

taken up by pancreatic tissue, but not by tumors, which increases the conspicuity of tumors (Fig. 36.6D). Problems for abdominal MRI appear with motion artifacts from respiration (if the patients cannot hold their breath for 15–20 s during scanning) as well as peristalsis. Tremendous advances have recently been made in pancreatic imaging with MRI. New developments allow faster imaging acquisition with higher signal-to-noise ratios and breath-hold images free of artifacts. MR examination for the detection of endocrine pancreatic neoplasms is optimally performed with a 1.5 Tesla gradient system. With the ongoing technical development already 3.0 Tesla machines are routinely used in abdominal imaging.

One of the typical imaging features of PNET is hypervascular enhancement. This often helps to distinguish them from the much more common pancreatic adenocarcinomas, which tend to be hypovascular in the arterial phase. Although PNETs are classically considered hypervascular in the arterial phase, the degree, uniformity, and timing of enhancement can be highly variable. Such pancreatic tumors may be distinguished from the surrounding organ on only one contrast-enhanced phase (Figs. 36.7 and 36.8). In fact, some PNETs may be seen best on venous phase images or can be masked in different perfusion stages and show isointense signal and enhancement characteristics similar to those of the normal pancreas after

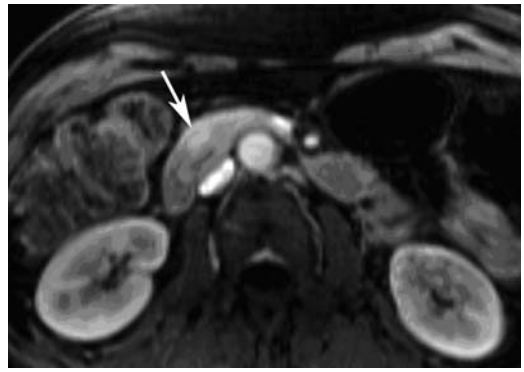

Fig. 36.8. Gadolinium-enhanced MRI image in the arterial phase shows a small, moderately hyperintense insulinoma in the pancreatic head without deformation of the contour. MDCT is false negative in this case.

contrast administration, being nearly invisible on all but unenhanced images. Different enhancement patterns of PNETs may aid in their detection and distinction from other pancreatic neoplasms. A characteristic ringlike enhancement is often seen on early or delayed contrast-enhanced images. Also, the uniformity of enhancement can be variable, with larger, more malignant lesions exhibiting more heterogeneous enhancement. Small lesions are often benign and homogeneous in enhancement.

Large PNET may show cystic or necrotic areas of nonenhancement, which sometimes occupy most of the lesion. Nonfunctioning PNETs are more often necrotic or cystic and present later, often with metastases at the time of diagnosis. Some lesions may, therefore, because of a cystic appearance, be misdiagnosed as intraductal papillary mucinous neoplasms, microcystic adenomas, or mucinous cystic neoplasms. Metastases from PNETs most frequently involve the liver [62] and peripancreatic lymph nodes (Fig. 36.6B–D). The signal characteristics of metastases tend to look like those of the primary lesion. Central necrosis often occurs as metastases grow. With increasing time and cost constraints it is often not possible to do both MDCT and MR imaging of pancreatic NET in every patient. Because of the rarity of neuroendocrine tumors and the rapid development of CT and MRI techniques, the best imaging techniques will remain difficult to define. In a side-by-side comparison, MDCT scanning is probably superior to MRI because of less motion artifacts and the superior 3D reconstruction available. MRI is the problem-solving tool after equivocal CT results regarding the presence of small tumors or liver metastases. Additionally MR avoids radiation exposure in these patients, who are often young and may require long-term imaging follow-up.

Digital Subtraction Angiography

MDCT and MRI are playing an increasingly important role, but angiography retains its place in clarifying equivocal lesions shown by other modalities. It may successfully localize tumors not otherwise demonstrated, although digital subtraction angiography (DSA) is now most often combined with a venous sampling examination (Table 36.1). The pancreas derives its blood supply from the celiac and superior mesenteric arteries (see Chapter 35). The diagnostic accuracy will be greatly increased if the pancreas can be examined in greater detail by more selective angiograms. An ideal pancreatic angiogram includes selective injections into the celiac axis, superior mesenteric artery, and splenic, gastroduodenal, dorsal pancreatic, and pancreaticoduodenal arteries.

The general celiac study is important because it demonstrates the vascular anatomy of the liver and pancreas and may reveal the presence of hepatic metastases. DSA, where available, can be very helpful, and magnification of photographic subtraction films may clarify doubtful lesions.

The most characteristic feature of a PNET at angiography is a dense, circumscribed, homogeneous capillary blush. This usually appears 2–4 s after the injection of contrast medium becomes most conspicuous between 4 and 8 s and may persist for 12–16 s. Features suggestive of malignancy include marked tortuosity of the feeding vessels, irregular tumor outline, arterial encasement, and venous obstruction.

When tumors are large, image analysis is somewhat easy. Hypervascular lesions or hypervascular tumors with central hypodense zones due to tumor necrosis are relatively specific for an islet cell tumor. However, making up the diagnosis may be difficult in small tumors. Arterial displacement of the intrapancreatic vessels and small homogeneously attenuated lesions with a fast washout are the more specific signs for a tumor. False-positive diagnoses of PNETs may be made by misinterpretation of vascular blushes due to normal duodenum, stomach, adrenal gland, and spleen. Hyperplastic lymph nodes, inflamed small bowel, or chronic pancreatitis may be other sources of error.

Arterial Stimulation with Venous Sampling

Angiography combined with intraarterial stimulation and venous sampling (ASVS) is a method for tumor “regionalization” in case of a hormone-secreting tumor (Table 36.1), which is too small to be diagnosed with other imaging modalities [65]. Over the last decade, ASVS has become increasingly popular due to its highly

sensitive localizing rates of up to 96% in some reports [66, 67].

The underlying principle of ASVS is to detect the area of hormone secretion by identifying the artery, which when infused with a substance stimulating tumor secretion (calcium gluconate in insulinoma, SACI test; secretin in gastrinoma, SASI test; see also Chapter 38), increases hormonal output with a positive gradient compared with baseline values.

In ASVS technique, under fluoroscopic guidance of the DSA, a catheter for the venous blood sampling should be hooked into the confluence of the liver veins. After obtaining an arteriogram of the abdominal aorta, a catheter should be placed selectively at proximal and distal splenic artery, gastroduodenal artery, right and left hepatic artery, and in all selectively catheterized pancreatic arteries.

Because of its invasiveness and cost ASVS is now reserved for rare cases with equivocal or contradictory CT, MRI, and EUS studies, especially before reoperation. In this scenario, ASVS is cost-effective.

In patients with biochemically confirmed hyperinsulinism but without circumscribed PNET, "Noninsulinoma Pancreatogenous Hypoglycemia Syndrome (NIPHS)"/"Adult Nesidioblastosis" (see Chapter 37) must be suspected. In these rare instances the SACI test is mandatory to confirm the tentative diagnosis and to guide surgery [68].

Transhepatic Peripancreatic Venous Sampling

Transhepatic peripancreatic venous sampling (TPVS) may be useful if the results of ASVS are contradictory and may be indicated before reoperation in selected patients with functioning pancreatic tumors nonlocalized by noninvasive localization techniques.

First, percutaneous catheterization of the portal vein is necessary. Then, sequential blood sampling of the portal vein and peripancreatic veins is performed. TPVS can even be combined with arterial stimulation. TPVS is powerful in localizing active endocrine tumors of the pancreas, with detection rates close to 100%. Even small amounts of secreted hormone can be detected, as the blood is directly taken from the possible peripancreatic tumor-draining veins.

However, transhepatic venous sampling is an invasive procedure and is technically demanding and time-consuming. Complications because of transhepatic puncture, such as arterial bleeding, hematoma, and damaging the bile duct may appear. TPVS should be reserved for the few cases of inconclusive ASVS before reoperation.

Radionuclide Imaging

It is well established that anatomical imaging techniques are almost always the initial tests for diagnosis, staging, surgery planning, and monitoring of response to treatment in oncology. Such mainly anatomy-based imaging techniques, however, may have some limitations. A lesion in the pancreas or in another part of the body on CT and/or MRI in a case of biochemically suspected PNETs does not mean that this lesion is necessarily indicative for a PNET [69]. On the other hand, the presence of a lesion in the pancreas does not mean that this is a solitary lesion, as PNETs may be multicentric. A whole-body evaluation is therefore essential for staging of the disease. Last but not least, size-based interpretation criteria of the lesions may lead to false-negative or false-positive results.

SST Receptor Scintigraphy

To overcome such limitations of radiological modalities, nuclear medicine techniques done with radiolabeled SST analogs have been suggested about two decades ago as unique diagnostic tools for PNETs. SRS with ^{111}In-labeled DTPA-D-Phe^{1}-octreotide (Octreoscan®, Mallinckrodt, Petten, the Netherlands) has already gained widespread acceptance as the imaging modality of choice in SST receptor-expressing tumors showing a high sensitivity (80–90%) and good specificity for detection of primary and metastatic lesions (Table 36.3) [70, 71]. The molecular basis for SST-receptor scintigraphy is the overexpression of SST receptors, mainly subtypes 2 and 5 on the tumor surface and the high binding affinity of the tracer [72, 73] in 80–90% of PNETs. With respect to patient management, Octreoscan proved to be able to detect

Table 36.3. Localization of pancreatic neuroendocrine tumors (PNET): Sensitivity of somatostatin receptor scintigraphy (SRS)

			Primary	Liver metastasis	Extrahepatic metastasis	
Author [ref]	Year	Tumor (*n*)	Sensitivity (%)	Sensitivity (%)	Sensitivity (%)	Method
Mirallé [32]	2002	Insulinoma (29)	47			SRS
			85			Endoscopic US
		Gastrinoma (26)	85		71[a]	SRS
			75		57	Endoscopic US
Chiti [103]	1998	Diverse (116)	62	90	90	SRS
			43	78	66	CT
			36	88	47	US
		Inactive NETs	79	89	89	SRS
			43	83	78	CT
			33	100	50	US
Lebtahi [104]	1997	Diverse (160)	68	94		SRS
			49	57		Diverse
Gibril [105]	1996	Gastrinoma (80)	58	92		SRS
			31	42		CT
			9	46		US
			30	71		MRI

[a]71% sensitivity of distant metastasis including liver metastasis.

previously unknown lesions modifying staging of the disease and changing the strategy of treatment in 25% of patients with PNETs [63, 74, 75]. In particular, the use of single photon emission CT (SPECT) and whole-body study may lead to detection of unknown tumor sites contributing to correct patient classification and appropriate therapeutic strategy in those patients [76]. On the other hand, based on the combined use of hybrid technology (CT/SPECT) SRS can detect more lesions which may be difficult to localize by single imaging techniques. This is especially true for gastrinomas, VIPomas, and glucagonomas. PNETs lacking SST receptors such as insulinomas may be negative on SRS.

Recently, further SST analogs have been developed. Among them, radiolabeled DOTA-Tyr(3)-octreotide, HYNIC-Tyr(3)-octreotide, DOTA-Tyr(3)-octreotate, and DOTA-lanreotide with different binding affinities to the SSTR subtype derivatives have shown considerable improvement of imaging results with increased tumor uptake [72, 77]. Because of superior imaging quality of these tracers there is increasing interest to use them whenever they are available.

Nevertheless, as generally known, all SPECT radiopharmaceuticals have limitations, such as limited spatial resolution and tumor to background ratio, that may hamper visualization of small tumor lesions in some patients, even in those tumors over-expressing high-affinity SST receptors [62]. This suggests the use of other imaging principles, such as positron emission tomography (PET).

Positron Emission Tomography

Based on its physical advantages, mainly high spatial resolution, PET is a widely accepted imaging approach in oncology. Fluorine-18 deoxyglycose (^{18}F-FDG) PET is the most commonly used tracer in nuclear oncology. Elevated uptake of ^{18}F-FDG has been demonstrated in various malignant primary tumors. However, many studies have demonstrated that ^{18}F-FDG is not always a suitable tracer for PNETs, based on the fact that PNETs may be well differentiated and do not show a high uptake of ^{18}F-FDG [76]. Other studies have shown that, nevertheless, ^{18}F-FDG may be successfully used for visualization of most aggressive PENTs with rapid cell proliferation [76, 78, 79]. Apart from some indications, ^{18}F-FDG PET is not indicated routinely in patients with neuroendocrine tumors.

One of the newer developments, ^{68}Ga-labeled DOTA-Tyr(3)-octreotide, has recently shown promising results in patients with NEPT, based on the high-affinity binding to the SST receptor subtype 2 in combination with PET technology, which offers higher resolution and better pharmacokinetics compared with the SPECT radiopharmaceuticals (Fig. 36.9) [80]. Recently, Gabriel et al. have shown a higher PET accuracy (96%) compared with SPECT (58%) and CT (75%) and provided more clinically relevant information in 14% of the NET patients. The combination of PET and CT yields the highest overall accuracy [81].

In recent years, another PET tracer, ^{18}F-L-dihydroxyphenylalanine (^{18}F-DOPA), has shown successful results in serotonin-positive PNETs. The overall sensitivity of ^{18}F-DOPA is 65% compared with Octreoscan at 57% and with conventional imaging techniques at 73% [82–84]. Interestingly, ^{18}F-DOPA seems to be superior to Octreoscan in the detection of bone metastases [85]. A novel study published in 2007 has demonstrated that ^{18}F-DOPA may be useful in the diagnosis of insulinomas, which are negative on CT and MRI [75]. ^{18}F-DOPA has the potential to become the functional imaging method in those patients in the future, in particular, by using hybrid PET/CT scanners. Nevertheless, it has been proposed that this method should be used only in patients with confirmed inappropriate insulin secretion, because of the physiological high tracer uptake of the normal pancreas.

Alternative positron-emitting tracers using different precursors for visualization of PNETs have been presented. One of these tracers is ^{11}C-5-hydroxytryptophan (^{11}C-5-HTP). Based on the capacity of PNETs for uptake, decarboxylation, transformation of 5-HTP into biogenic amines, and finally being irreversibly trapped by serotonin-producing tumors, ^{11}C-labeled 5-HTP is sensitive for small tumor lesions by PET imaging [86]. However, with respect to this tracer much work still needs to be done before general recommendations can be made.

The Value of Imaging of PNETs for the Endocrine Surgeon

The diagnosis of PNET is based on different examinations that vary according to the type

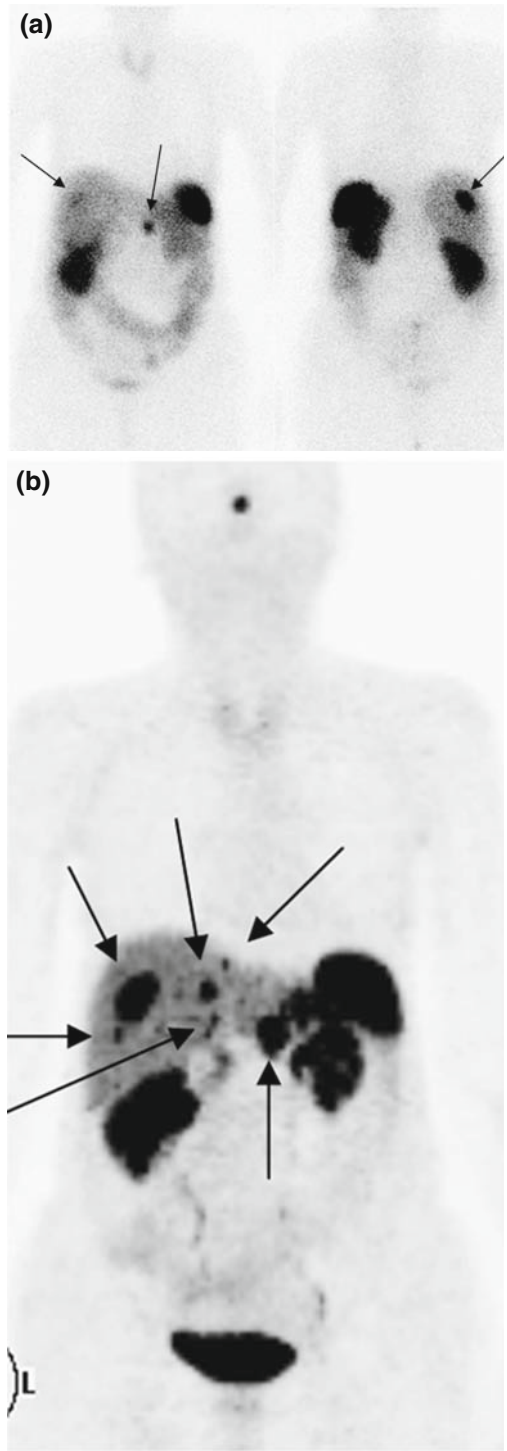

Fig. 36.9. Gastrinoma with multiple metastasis. (**A**) ^{111}In-labeled DTPA-D-Phe^{1}-octreotide (Octreoscan®) detects more distant lesions than (**B**) ^{68}Ga-labeled DOTA-Tyr(3)-octreotide.

and the site of the tumor. The fundamental diagnostic approaches are *medical history and clinical examination*. Any attempt to localize functional tumors [which are in the majority small (insulinoma, gastrinoma)] by EUS and CT or MRI should proceed only after the clinical diagnosis has been confirmed biochemically.

Rare functional endocrine tumors (vipoma, glucagonoma, somatostatinoma) and *nonfunctional* PNETs are usually more than 5 cm. In general imaging studies do not help to "find" the tumor but help to exclude local malignant growth, lymph node involvement, and distant metastases.

It is impossible to plan the management of patients suspected to be affected by neuroendocrine tumors without performing *functional (radionuclide) imaging*. These techniques help to reveal the endocrine nature of the tumor and help to determine metastatic spread (liver and/or extraabdominal metastases).

If ever possible the results of all imaging studies available should be discussed together with the radiologist and the nuclear medical physician under the aspects of clinical and biochemical work up.

The indication for surgery and the surgical strategy (tumor enucleation, limited or extended resection – distal pancreatic resection, pancreatico-duodenal resection, debulking) always depend on the biological behavior and the localization of the tumor.

Surgical excision is the treatment of choice for all islet cell tumors of the pancreas. For years the practice has been an "open" surgical approach (gold standard). This includes a complete exploration of all parts of the pancreas through an extended midline or transverse subcostal incision with bidigital palpation and IOUS to rule out multiple tumors and to demonstrate the relationship of the lesion to important vascular structures and to the pancreatic duct. If malignancy is suspected, adequate lymph node dissection is mandatory.

The fast development of various new "morphological" and "functional" pancreatic imaging techniques and their increasing preciseness allow "limited" explorations. EUS in combination with one other imaging procedure (3-phasic multidetector CT or gadolinium-enhanced MRI at a 1.5T MR unit) also detects small tumors (insulinoma, gastrinoma) in all parts of the pancreas. CT or gadolinium-enhanced MRI provides precise anatomical localization independent of the size. The overall detection rate of duodenal wall gastrinomas is very low. Therefore the localization of small duodenal gastrinoma may raise problems. In combination with SRS these procedures allow an exact staging of the tumor prior to surgery.

"Minimally invasive (endoscopic) surgery" is becoming more and more attractive in the treatment of PNETs. However, up to now, no criteria for patient selection for endoscopic surgical procedures have been defined yet with special regard to the management of sporadic, hereditary, solitary, and multiple and malignant PNETs [87].

A confident anatomical localization within the pancreas (size, relation to the pancreatic duct) and careful staging (extent) of the PNET are the keys to the success and therefore prerequisites if endoscopic procedures are considered.

The option applying IOEUS and the experience with this technique are prerequisites for endoscopic surgery. Due to the lack of tactile sensation during endoscopic surgery IOEUS is mandatory to localize the tumor before endoscopic enucleation or resection.

Selective enucleation is the treatment of choice in localized insulinomas if anatomically suitable (cave: pancreatic duct) [88]. Insulinomas in the pancreatic tail are in the majority of the patients better treated by spleen/pancreas-preserving distal pancreatic/tail resections [89].

Safe indications for endoscopic enucleation seem to be sporadic, solitary superficial, or pedunculated insulinomas of all pancreatic regions. Lesions localized in the pancreatic tail or those with a short distance to the main pancreatic duct [32] may be removed by spleen-preserving endoscopic distal pancreatic/tail resections.

Insulinoma localized deeply in the pancreatic head or dorsally may require conversion to open surgery when the operation cannot be performed safely.

Unlocalized or multiple insulinomas necessitate extended exploration of the whole gland. Under these circumstances "open" surgery is still favored by the majority of the endocrine surgeons. However, a laparoscopic approach may be applied by a surgeon with high experience in endoscopic procedures and in IOEUS.

Gastrinomas in the pancreatic head should be enucleated and distal pancreatic resection

should be performed for caudally located tumors. Duodenotomy with careful palpation of the duodenal wall is an integral part of all gastrinoma operations and therefore has to be performed routinely to detect small submucosal duodenal gastrinomas not localized preoperatively. A lymph node dissection has to be performed routinely [90].

Final recommendations for laparoscopic surgery in gastrinoma cannot be given at this time. The value of laparoscopic surgery in gastrinoma is questionable and may be hazardous because frequently the primary tumor is not seen on preoperative imaging studies and the tumors are located in the submucosa of the duodenum. The laparoscopic approach may be performed only when the tumor is preoperatively well localized in the pancreatic head or in the anterior duodenal wall and the surgeon is familiar with techniques of endoscopic peripancreatic lymphadenectomy.

Multiple tumors are the rule in MEN 1 and may be located in all parts of the pancreas. Surgical intervention is currently recommended for PETs >10–20 mm to avoid metastases [50, 91]. The recommended surgical procedure is spleen-preserving distal pancreatectomy and enucleation of any tumors in the head or uncinate process. A duodenotomy is necessary when the serum gastrin levels are elevated and a secretin test is positive. A peripancreatic lymph node dissection is performed in patients with duodenal gastrinomas and in rare patients with malignant insulinoma.

In selected patients with MEN 1 a spleen-preserving distal pancreatectomy and an enucleation of PNETs localized in the pancreatic head may be performed laparoscopically.

Curative surgery is always recommended in "rare functioning and nonfunctioning tumors" whenever feasible after careful symptomatic control of the clinical symptoms [51, 92]. Somatostatinoma, glucagonoma, and vipoma are more than 90% malignant, located in the pancreatic body or tail, and at the time of diagnosis are ≥20 mm.

The minority of nonfunctioning PNETs is ≤20 mm and are localized in the pancreatic head. Curative surgery should include oncological resection with lymphadenectomy.

If malignancy is suspected and/or the tumor ≥20 mm and a curative procedure predicted, a radical open procedure with lymph node dissection should be favored. However, endoscopic procedures may be selected for patients with a palliative intent or if one can achieve the same radical extent of surgery (primary tumor, lymph nodes) as applying an open procedure.

In patients with advanced stages of functioning tumors, debulking surgical strategies have a major role. In selected patients a palliative endoscopic pancreatic tail or distal pancreatic resection (including the spleen) may be discussed.

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37

Diagnosis and Management of Hyperinsulinemic Hypoglycemia

Adrian Vella, Geoffrey B. Thompson, and F. John Service

Introduction

The first case of hyperinsulinism was reported in 1927, at the Mayo Clinic, when an orthopedic surgeon presented with episodes of severe hypoglycemia due to a malignant pancreatic islet cell tumor [1]. Following his death, postmortem extracts of liver metastases caused marked hypoglycemia when injected into laboratory animals. In 1929, Graham in Toronto performed the first curative operation for a benign insulinoma. Subsequent to the identification of insulinoma as the source of excessive insulin secretion, the recognition that food deprivation provoked hypoglycemia led to the evolution of the prolonged fast as the chief diagnostic test for hypoglycemia in the absence of a documented, spontaneous episode.

Whipple's Triad

Many common and nonspecific symptoms are incorrectly attributed to hypoglycemia. Therefore, if one is to correctly attribute these symptoms to hypoglycemia, a low plasma glucose level must be documented at the time that spontaneous neuroglycopenic symptoms occur. Subsequently, one must demonstrate that such symptoms are relieved through the correction of the low glucose level ($<$50 mg/dl). This is Whipple's triad, i.e., symptoms occur at the time of hypoglycemia and resolve with the administration of glucose [2]. Reflectance meter measurements are not reliable in these situations due to their potential inaccuracy when glucose levels are $<$80 mg/dl and can provide misleading information.

The measurement of plasma glucose levels is not always feasible when spontaneous symptoms occur during activities of ordinary life. If a hypoglycemic disorder is suspected, the physician may decide to undertake provocative testing in the hope of replicating the circumstances during which hypoglycemia occurs. Such testing may involve prolonged fasting or, if hypoglycemia occurs after meal ingestion, a mixed meal test.

Biochemical criteria for the diagnosis of a hyperinsulinemic hypoglycemic disorder in the presence of documented blood glucose levels below 50 mg/dl include concomitant insulin levels equal to or greater than 3 μU/ml and an elevated C-peptide ($\geq$200 pmol/l). The potential presence of insulin secretagogues must be excluded by use of an oral hypoglycemic agent screen that reliably detects third generation sulfonylureas, and glitinides. Although insulin and C-peptide levels are secreted in equimolar amounts, the different half-lives (4–5 min for insulin, $>$14 min for C-peptide) explain the discrepancy often seen between values. The insulin/C-peptide ratio is the same for people with insulinoma as it is for normal subjects and, therefore, not useful for confirming or excluding the

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presence or absence of a hypoglycemic disorder. The insulin/glucose ratio and various iterations of this qualitative measure of insulin action such as the homeostasis model assessment (HOMA) play no role in the assessment of patients with a suspected hypoglycemic disorder.

Hypoglycemic Disorders – Classification and Causes

Classifications of hypoglycemic disorders that attempt to differentiate between disorders based on the timing of hypoglycemia in relation to meals (fasting versus postprandial hypoglycemia) may create difficulty because it is sometimes difficult to differentiate between the two. In addition, some causes of hypoglycemia cause both fasting and postprandial symptoms. A classification we prefer recognizes that persons who appear healthy have hypoglycemic disorders that differ from those persons who are ill [3] (Table 37.1).

In healthy adult patients with a history of episodic neuroglycopenia, the causes of hyperinsulinemic hypoglycemia may encompass the following conditions: factitial hypoglycemia from insulin or sulfonylurea use, insulinoma, noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS), and insulin autoimmune hypoglycemia.

In contrast, a patient with coexisting disease may develop hypoglycemia because of the underlying disease. In such situations, it may be sufficient to recognize the underlying disease and its association with hypoglycemia and to take action to minimize recurrences. Hospitalized patients are also at risk for iatrogenic hypoglycemia and other prescribing errors.

Causes of Endogenous Hyperinsulinemic Hypoglycemia

Insulinoma

Insulinomas are the most common functioning islet cell tumors. More than 80% are solitary, benign tumors with an indolent course. Indeed, patients may tolerate symptoms of hypoglycemia for many years prior to seeking medical attention [4]. The patients seen at our institution between July 1982 and October 2004 experienced a mean time from symptom onset to diagnosis of 50 months [5]. A single adenoma is found in the overwhelming majority of patients with sporadic insulinomas.

Noninsulinoma Pancreatogenous Hypoglycemia Syndrome

NIPHS is a recently recognized clinical entity where patients experience neuroglycopenic symptoms 2–4 h postprandially and generally not in the fasting state [6]. These patients exhibit positive responses to the selective arterial calcium stimulation test indicative of beta-cell hyperfunction. Gradient-guided partial pancreatectomy leads to amelioration of the hypoglycemic symptoms. Pancreatic tissue from these patients shows evidence of islet hyperplasia and nesidioblastosis. No disease-causing mutations in the *Kir6.2* and *SUR1* genes (associated with familial persistent hyperinsulinemic hypoglycemia of infancy) have been associated with this condition (Table 37.2).

A similar presentation is being increasingly recognized in patients who have undergone bariatric surgery [7]. Islet cell tumors may accompany the hyperplastic changes in a significant minority of patients. Moreover, patients afflicted with postprandial hypoglycemia after Roux-en-Y gastric bypass tend to be predominantly female. This is very dissimilar to the male:female ratio encountered in NIPHS.

We have seen the rare patient who develops organic hyperinsulinism immediately after undergoing gastric bypass surgery. This implies that the affected patient has an insulinoma and not postbypass hypoglycemia, as this disorder presents later. It is likely that with gastric restriction, the insulinoma patient is unable to prevent hypoglycemia due to an inability to consume sufficient glucose to overcome the dysregulation in insulin secretion.

It is important to note that there has been controversy regarding the pathophysiology of this disorder. Proponents of the view that

Table 37.1. Hyperinsulinemic hypoglycemia in adults (differential diagnosis)

Diagnostic interpretation	Symptoms or Signs	Glucose (mg/dl)	Insulin (μU/ml)	C-peptide (pmol/l)	Proinsulin (pmol/l)	B-hydroxybutyrate (mmol/l)	Glucose response to glucagon (mg/dl)	Sulfonylurea/ meglitinide in serum	Insulin antibodies
Normal	No	40–60	<3	<200	<5	>2.7	<25	No	Neg
Insulinoma/ NIPHS	Yes	≤45	≥3	≥200	≥5	≤2.7	>25	No	Neg
Insulin factitious	Yes	≤45	>3	<200	<5	≤2.7	>25	No	Neg/Pos
Sulfonylurea factitious	Yes	≤45	≥3	≤200	≥5	≤2.7	≥25	Yes	Neg
IAS*	Yes	≤45	>>3	>>200	>>5	<2.7	>25	No	Pos

*Insulin autoimmune hypoglycemia.

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Table 37.2 Adult nesidioblastosis

- Postprandial hyperinsulinemic hypoglycemia
- More common in males(NIPHS)
- More common in females (post Roux-en-Y gastric bypass)
- Negative 72-h fast
- Negative perioperative radiologic localization studies
- Positive selective arterial calcium stimulation test
- Relief of symptoms by gradient-guided partial pancreatectomy
- Islet hypertrophy and B cells budding from acinar ducts

Source: Reprinted with permission from Thompson GB, Grant CS, Farley DR. Surgical treatment and management of insulinomas. In: Pollock RE, Curley SA, Ross MI, Perrier ND, editors. Advanced therapy in surgical oncology. Ontario, Canada: BC Decker Inc., (in press).

hypoglycemia is due to the unopposed action (via reduced caloric intake) of premorbid hypertrophic islets characteristic of obesity fail to account for the interval of months to a few years between the gastric bypass surgery and the development of hypoglycemia. This is especially noteworthy given that the defective insulin action evident preoperatively is restored to normal shortly after bariatric surgery [8].

Uncertainty about the existence of an anatomical cause of postgastric bypass hypoglycemia (if one can discount the islet cell tumors encountered in some patients with this condition) has given voice to argument that postgastric bypass hypoglycemia may represent a functional problem arising in part from excessive GLP-1 secretion after meal ingestion. GLP-1 is an incretin and is thought to stimulate islet neogenesis, as well as inhibit β-cell apoptosis [9]. The effect of GLP-1 on insulin secretion has been considered to be glucose-dependent and, therefore, unlikely to cause hypoglycemia. While the elevated GLP-1 concentrations seen in patients after bypass surgery may be a reasonable explanation for some of the abnormalities seen in affected patients, many questions remain unanswered. Elevated GLP-1 may merely be a marker of the rapid rate of meal appearance in the distal intestine. Also, since GLP-1 elevations are commonly observed in the absence of hypoglycemic symptoms after bypass surgery, other factors are necessary to explain the occurrence of hypoglycemia in a subset of bariatric patients.

Insulin Autoantibody Hypoglycemia

This is a rare disorder where hyperinsulinemic hypoglycemia is associated with high titers of antibodies to human insulin that occur in the absence of prior exposure to exogenous insulin. Hypoglycemia occurs in the presence of normal pancreatic islets because the insulin autoantibodies initially bind secreted insulin and then release this bound insulin independently of prevailing glucose concentrations. The hypoglycemia is not associated with any change in sequentially measured titers of insulin antibodies. Measurement of insulin antibodies during the evaluation of a patient with hypoglycemia is required to make the diagnosis, although very high serum insulin concentrations are unique to this disorder [10].

Diagnostic Tests Used in the Evaluation of Suspected Hypoglycemic Disorders

The 72-H Fast

The 72-h fast is the classic diagnostic test for hypoglycemia. The fast may be conducted to establish that hypoglycemia is truly the basis for the patient's symptoms if Whipple's triad has not already been demonstrated. On the other hand, if hypoglycemia at the time of symptom onset has been demonstrated together with symptom relief after correction of hypoglycemia, then the rationale for conducting a 72-h fast would be established if endogenous hyperinsulinemia is the cause of the patient's hypoglycemia.

In a fast performed for the first purpose, Whipple's triad must be demonstrated. Measurement of β-cell polypeptide products and screening for the presence of sulfonylureas (or other hypoglycemic agents) in the serum provide adjunctive data. In patients who do not exhibit symptoms or signs of hypoglycemia and in those without severely depressed plasma glucose concentrations (below 45 mg/dl), the fast should be terminated at 72 h unless there is a progressive rise in the concentrations of beta-hydroxybutyrate (BOHB) a biomarker for insulinopenia. No patient with organic hyperinsulinism, in our experience, has been detected beyond this time threshold.

The decision to end the fast may not be easy to make when documentation of Whipple's triad is the goal. Some healthy patients may have plasma glucose levels in the range of 40 mg/dl without symptoms or signs of hypoglycemia (especially young female athletes). On the other hand, other subjects may experience the symptoms they experience in ordinary life. In such instances, the attribution of symptoms to hypoglycemia is difficult, especially if all additional measurements made during fasting are normal. Careful examination and testing for subtle signs or symptoms of neuroglycopenia should be conducted repeatedly when the patient's plasma glucose is in the hypoglycemic range. To end fasting solely on the basis of low plasma glucose levels in the absence of symptoms or signs of hypoglycemia jeopardizes the possibility of discriminating between normal persons and those with hypoglycemia not mediated by insulin.

Patients with insulinomas have insulin concentrations that rarely exceed 100 μU/ml. Concentrations greater than 100μU/ml suggest recent insulin administration or the presence of insulin antibodies. Measurement of plasma β-hydroxybutyrate at the end of a fast can be used as an insulin surrogate. This is because hepatic ketone production is extremely sensitive to insulin and is suppressed by hyperinsulinemia. Another insulin surrogate is the response of plasma glucose to intravenous glucagon at the end of the fast. Insulin suppresses glycogenolysis and stimulates glycogen synthesis. A plasma glucose increment of 25 mg/dl or greater above the terminal fasting plasma glucose suggests the presence of hyperinsulinemia to a degree that prevented glycogenolysis during the fast [11].

Insulin surrogates (β-hydroxybutyrate and glucose response to intravenous glucagon) are interpretable when the plasma glucose is 60 mg/dl or lower at the end of the fast. These surrogates are useful in determining that an insulin-like factor is the cause of hypoglycemia in patients with neuroglycopenia when insulin is undetectable at the time of hypoglycemia. A rising concentration of β-hydroxybutyrate may indicate a negative fast [12].

Screening for the presence of oral hypoglycemic agents (during the fast and at the time of hypoglycemia) is an essential component of the prolonged supervised fast. The pattern of plasma glucose and β-cell polypeptides produced by secretagogues that stimulate endogenous insulin secretion cannot be distinguished from that observed in persons with insulinoma.

Mixed Meal Test

For persons with a history of neuroglycopenic symptoms within 5 h of food ingestion, a mixed meal test may be a useful provocative test. The test is considered positive if the patient experiences neuroglycopenic symptoms when concomitant plasma glucose is low ($\leq$50 mg/dl). There are no standards for the interpretation of levels of β-cell polypeptides measured during this test. A positive mixed meal test, like a positive 72-h fast, does not provide a diagnosis, only biochemical confirmation of the history. Because patients with insulinoma may have neuroglycopenic symptoms after meals and, in some instances, only after meals, patients with a positive mixed meal test may require a prolonged (72-h) fast. In patients with a positive mixed meal test, with a history of neuroglycopenia postprandially confirmed biochemically and a negative 72-h fast, the possibility of NIPHS should be considered [6]. These patients should undergo selective arterial calcium stimulation [13]. The 5-h oral glucose tolerance test has no role as a diagnostic test for hypoglycemia because a substantial percentage of healthy persons may have a plasma glucose nadir of 50 mg/dl or lower [14] without evidence of neuroglycopenia [15].

Insulin Antibodies

Insulin antibodies may be present in patients using (or abusing) animal insulin. Patients who use human insulin usually have no detectable insulin antibodies since this is less antigenic than the forms derived from animals. On occasion insulin antibodies are present in high titer and are pathogenic, causing insulin autoimmune hypoglycemia. Affected patients usually have no prior exposure to insulin [10]. This entity is more prevalent in Asian populations.

Localization Procedures

As with most endocrine disorders documentation of abnormal function, i.e., hyperinsulinemic hypoglycemia is essential prior to embarking on

anatomic localization. The choice of imaging modalities has been the subject of much debate. We believe that the choice is dependent on the expertise and technology available at a particular center as well as the patient characteristics (previous abdominal surgery, obesity, etc.).

Transabdominal Ultrasonography

This method is noninvasive, relatively inexpensive, and anatomically precise. However, it is very dependent on the expertise of the operator. Its ability to reliably visualize the pancreas in obese individuals is limited. Most insulinomas are hypoechoic with a distinct interface between the normal pancreas and the tumor. They are most likely to be visualized when embedded within the pancreas. If situated on the pancreatic surface, the tumor is often indistinguishable from surrounding fat. Ultrasound examination should also include visualization of the uncinate process behind the superior mesenteric vein.

Endoscopic Ultrasonography

Endoscopic ultrasonography overcomes some of the limitations imposed by body habitus or gastrointestinal tract air on transabdominal ultrasonography. It is most likely to localize tumors in the head of the pancreas and is less likely to visualize tumors in the body and tail [16]. Again the technique is highly dependent on operator expertise. Given the upper gastrointestinal anatomy after Roux-en-Y gastric bypass surgery, the technique is of little use in such patients.

Intraoperative Ultrasonography

Intraoperative ultrasonography overcomes the limitations imposed by body habitus or air within abdominal organs. It is invaluable in localizing islet tumors, especially when multiple tumors may be present (as in multiple endocrine neoplasia). The relationship of the tumor to the ducts and adjacent blood vessels can also be determined [17].

Computed Tomography

Computed tomography (CT) is safe, relatively simple to perform, and operator independent. In morbidly obese patients it is the first-line imaging modality of choice. Previously reported sensitivities for this test ranged from 20 to 40%. The advent of spiral CT together with dynamic imaging of intravenous bolus infusion of contrast has produced a remarkable increase in the sensitivity of CT for the detection of insulinoma with reported sensitivities ranging between 60 and 90% [18]. CT imaging is also helpful in the detection of metastatic disease (Figs. 37.1 and 37.2).

Arteriography

Previously considered to be the gold standard for the localization of insulinomas, the use of arteriography has declined due to improvements in alternative imaging modalities. It is invasive, expensive, and requires considerable technical expertise to perform and interpret. Currently arteriography is utilized solely in our practice as part of the selective intraarterial calcium stimulation procedure described below.

Selective Arterial Calcium Injection

The diagnosis of a hypoglycemic disorder should be made biochemically prior to attempts at localization. However, since the description of NIPHS as a clinical entity, this test has been increasingly used as a diagnostic test. Previously, the knowledge that calcium infusion can stimulate insulin secretion from an insulinoma together with selective arterial injection and venous sampling had been used to regionalize insulinomas [19] (Fig. 37.3).

In this procedure, a catheter is sequentially inserted into the gastroduodenal, superior mesenteric, and splenic arteries. Calcium is then injected into these arterial territories. The second catheter is placed in the right hepatic vein via the inferior vena cava and is used to sample insulin concentrations. Following the intraarterial injection of calcium, a 2- to 3-fold step-up of insulin when measured 20, 40, and 60 s after calcium injection in the venous effluent will regionalize the hyperinsulinism to the head of the pancreas (gastroduodenal artery), the uncinate (superior mesenteric artery), and the body or tail (splenic artery). A solitary insulinoma can produce responses in adjacent territories if it is located in the watershed of overlapping territories.

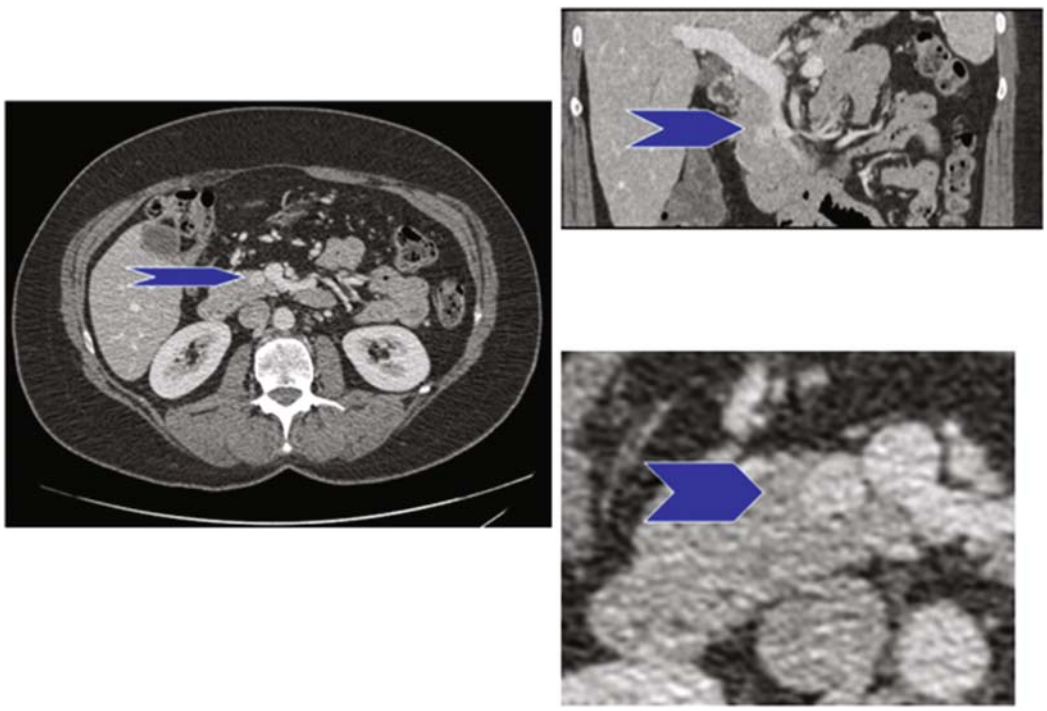

Fig. 37.1. Late arterial, early venous phase of spiral CT demonstrating vascular blush in the pancreatic uncinate adjacent to superior mesenteric vein. Reprinted with permission from Thompson GB, Grant CS, Farley DR. Surgical treatment and management of insulinomas. In: Pollock RE, Curley SA, Ross MI, Perrier ND, editors. Advanced therapy in surgical oncology. Ontario, Canada: BC Decker Inc, (in press).

Patients with NIPHS exhibit a similar response to intraarterial calcium injection. Although NIPHS is assumed to be a diffuse process with irregular dysplastic islets and nesidioblastosis (Fig. 37.4), a response is not invariably seen in all three regions of the pancreas. This may reflect individual variation in blood supply which may falsely regionalize the site of hypersecretion. An arteriogram obtained at the same time allows assessment of the pancreatic circulation and may help explain such aberrations. It is important to note two important assumptions on which this test is based. One is that a pancreatic vascular territory that exhibits an abnormal response to intraarterial calcium is unique to individuals with a hypoglycemic disorder. The second is that an abnormal response is reproducible. However, our anecdotal experience with repeated testing in a few patients is that the responses do not vary. Given the expense and the invasiveness of this test, the studies necessary to accept or refute these assumptions have not been undertaken.

Management

After hyperinsulinemic hypoglycemia is documented, either spontaneously or after a provocative test, the next step is to determine whether iatrogenic causes, underlying disease or surreptitious use of hypoglycemic agents, might explain these episodes. Assuming that this is not the case, attempts should be made to document a source for abnormal insulin secretion. Assuming noninvasive imaging is negative, endoscopic ultrasonography and/or selective arterial calcium injection may be required.

In patients with postbariatric hypoglycemia the decision to proceed with partial pancreatectomy must be balanced against the future risk of diabetes, pancreatic exocrine insufficiency, and other complications of surgery. Some patients have experienced short- and long-term symptomatic relief when using acarbose or somatostatin.

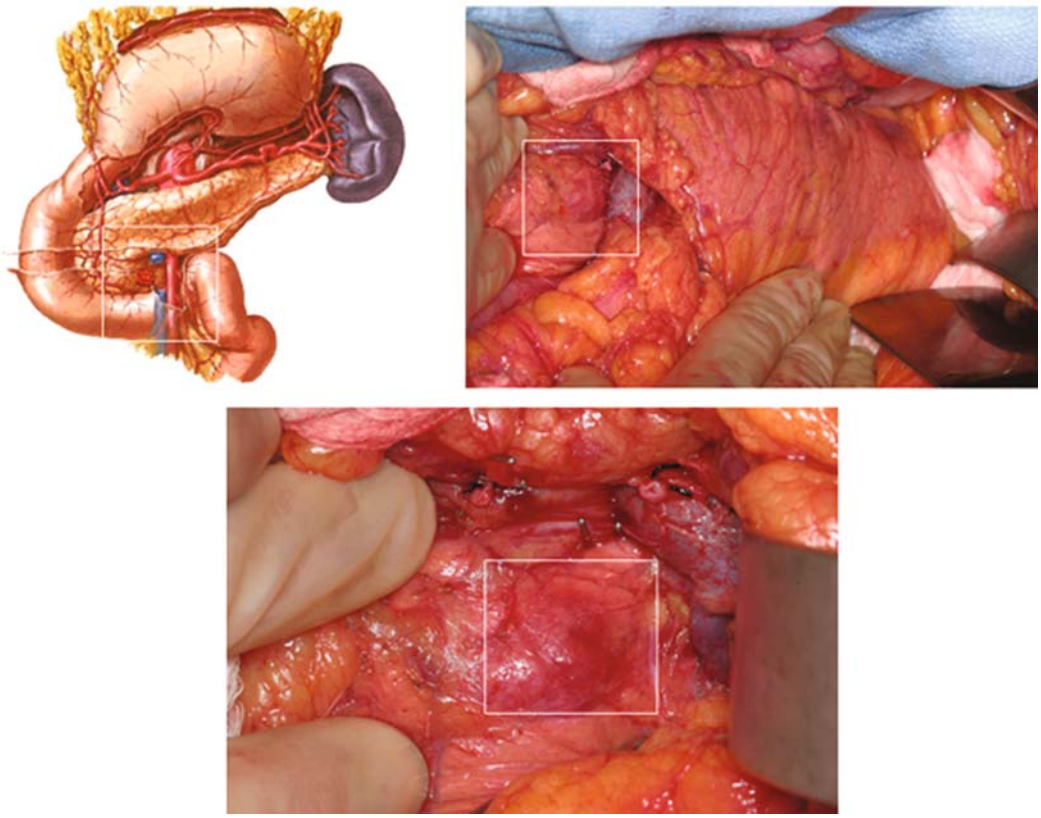

Fig. 37.2. Corresponding gross photographs to spiral CTs in Fig. 37.1. Reprinted with permission from Thompson GB, Grant CS, Farley DR. Surgical treatment and management of insulinomas. In: Pollock RE, Curley SA, Ross MI, Perrier ND, editors. Advanced therapy in surgical oncology. Ontario, Canada: BC Decker Inc. (in press).

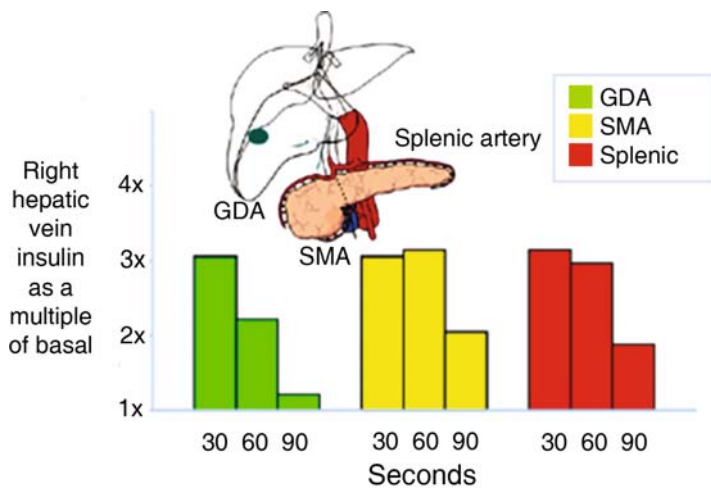

Fig. 37.3. Results of selective arterial calcium stimulation test in patient with NIPHS. Note positive gradients in all three arterial distributions. Reprinted with permission from Thompson GB, Grant CS, Farley DR. Surgical treatment and management of insulinomas. In: Pollock RE, Curley SA, Ross MI, Perrier ND, editors. Advanced therapy in surgical oncology. Ontario, Canada: BC Decker Inc. (in press).

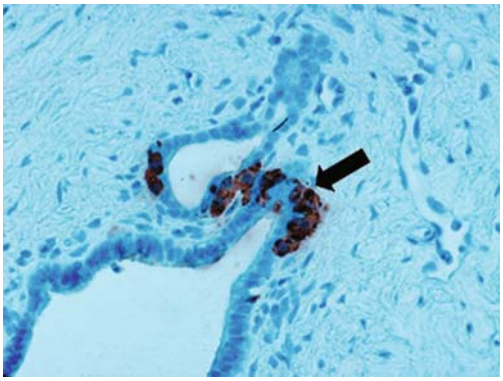

Fig. 37.4. Immunostain for insulin demonstrating β cells budding off an exocrine duct (nesidioblastosis). Reprinted with permission from Thompson GB, Grant CS, Farley DR. Surgical treatment and management of insulinomas. In: Pollock RE, Curley SA, Ross MI, Perrier ND, editors. Advanced therapy in surgical oncology. Ontario, Canada: BC Decker Inc. (in press).

Surgical enucleation is the treatment of choice for insulinoma. Cure should be expected in patients without the multiple endocrine neoplasia type 1 (MEN1) syndrome. In such patients there is only a 7% recurrence rate [5]. Many patients with MEN1 have multicentric benign disease as well as a higher incidence of recurrence (21%). Conservative pancreatic resection in this setting is likely to predispose to recurrent disease. Distal subtotal pancreatic resection to the level of the portal vein combined with enucleation of tumors in the head of the pancreas (guided by intraoperative ultrasonography) whenever possible is the optimal treatment. Preservation of endocrine and exocrine pancreatic function may not be possible in these situations [17].

Management of Endogenous Hyperinsulinism – A Surgeon's Perspective

Over 400 patients have undergone surgical management for endogenous hyperinsulinism at Mayo Clinic since the first case was reported by Wilder and Mayo in 1926 [1]. This experience has afforded us a wealth of clinical material, from which has evolved our present day practice. Obviously, much has changed, yet much remains the same.

The hallmark underlying successful surgical management of insulinoma and NIPHS is certainty with regard to the preoperative diagnosis. The last three decades at our institution have seen a transition from the controlled, in-hospital, 72-h fast to the more common and cost-effective, outpatient evaluation. The patient, accompanied by a friend or family, is provided with a card to obtain a standardized "end-of-fast" hypoglycemia bundle when they present to our endocrine testing center (ETC) during the day, or to the emergency department at night, with neuroglycopenic symptoms. Satisfying Whipple's triad is no less important today than it was in the early half of the twentieth century. The end-of-fast studies obtained during a spontaneous hypoglycemic event or at the end point of a controlled fast can only be interpreted accurately when true neuroglycopenia is present – the hallmark of organic hyperinsulinism. When the diagnosis is secure, then, and only then, is it appropriate to proceed with localization studies [20, 21]. With yearly advances in the quality of cross-sectional imaging, incidental findings can lead the unsuspecting surgeon without a definitive diagnosis of organic hyperinsulinism down the primrose path to disaster.

Intraoperative pancreatic ultrasonography was perhaps the greatest advancement in insulinoma localization in the 1980 s. In a large consecutive series of patients at Mayo, both its sensitivity and its positive predictive value were 97% [21, 22]. That, coupled with an experienced surgeon, led to success in nearly all patients with sporadic, solitary insulinomas. Today, however, our practice is encumbered with patients who manifest postgastric bypass hypoglycemia [7, 23–28]; most are females following Roux-en-Y gastric bypass for medically complicated obesity. Still others are males with NIPHS, many of whom have previously undergone one form or another of upper gastrointestinal surgery excluding bariatric surgery. Some are MEN1 patients with multiple islet cell tumors. Rarely, we see sporadic patients with multiple islet cell tumors, although these tumors often congregate close to one another in a given pancreatic region. This spectrum of disease, and the well-described overlap of fasting and postprandial hypoglycemia, has made

preoperative localization or regionalization, the rule, and not the exception, in our practice today.

Transabdominal ultrasound and spiral CT [29] with a pancreatic protocol have accurately identified two thirds of solitary sporadic insulinomas in our practice. Endoscopic ultrasonography has been very successful at detecting insulinomas (sensitivity >90%) [16, 30–32], especially those in the pancreatic head and uncinate. In some centers, this is the principal imaging modality employed. It has the advantage of being able to biopsy an indeterminate pancreatic lesion when in question. For patients with occult insulinomas and suspected NIPHS, selective arterial calcium stimulation with hepatic vein insulin sampling (SACST) provides useful information in planning and directing the operative procedure by regionalizing the site or sites of insulin overproduction. In approximately 60% of these studies, when an insulinoma is the cause, a tumor blush may be apparent, thus converting the test from a regionalizing to a localizing procedure. With this information in hand, one can then perform a gradient-guided resection with a high likelihood of success, provided that the preoperative diagnosis was indeed accurate [6, 7]. This is very different from the blind distal resections previously espoused, but now condemned for its high failure rate and disastrous operative and metabolic consequences it created when further surgical intervention ensued [33].

In our modern series of sporadic insulinomas, two thirds have been amenable to enucleation (Fig. 37.5) and one third to distal pancreatic resection, with or without splenic reservation. Three percent have required Whipple resections for large or malignant tumors in the pancreatic head. Twelve percent of the procedures were reoperations procured from outside referrals. Fewer than ten laparoscopic procedures have been successfully carried out at Mayo Clinic to date for organic hyperinsulinism [21, 34].

With this surgical approach, we have seen no perioperative deaths, and 82% were deemed complication free. Despite meticulous attention to detail, avoidance of unipolar cautery and extensive suturing, as well as the liberal use of intraoperative ultrasound to map out the pancreatic duct, we experienced, and continue to experience, a pancreatic fistula rate of approximately 18%. This, we believe, is about as good as it gets in a large experience, when you create holes in or divide pancreatic parenchyma. Octreotide, fibrin glue, staplers, and various modern modalities employing thermal- or ultrasound-generated energy have, to the best of our knowledge, not cut that rate any lower in all but the smallest and most anecdotal series reported to date.

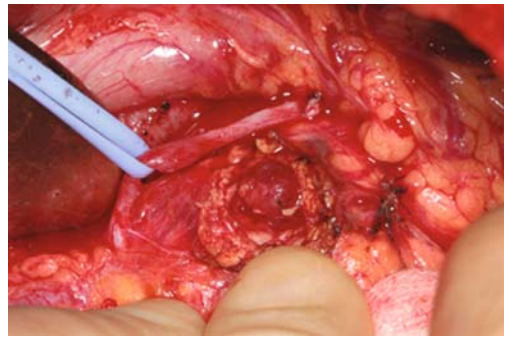

Fig. 37.5. Enucleation of islet cell tumor in the head of the pancreas just deep to the gastroduodenal artery. Reprinted with permission from Thompson GB, Grant CS, Farley DR. Surgical treatment and management of insulinomas. In: Pollock RE, Curley SA, Ross MI, Perrier ND, editors. Advanced therapy in surgical oncology. Ontario, Canada: BC Decker Inc. (in press).

Finally, we come to the role of laparoscopic surgery for insulinoma and nesidioblastosis (whether from NIPHS or from postgastric bypass hypoglycemia) [34, 35–49]. The final verdict is not yet in. Obviously, the pancreas is a deeply seated, retroperitoneal organ, situated far from the skin surface. A minimally invasive approach would obviate the need for a large, painful transverse or midline abdominal incision: a key factor in the success and application of other minimally invasive intraabdominal procedures (gastric bypass, Nissen fundoplication, adrenalectomy, cholecystectomy). Since most insulinomas are small (<2 cm) and benign (>90%), a major goal of insulinoma surgery is organ preservation. Enucleation is the surgical procedure of choice for these often encapsulated or pseudoencapsulated tumors. Enucleation requires a near-bloodless field, fine instruments, and punctilious attention to detail. With the available technology in 2008, these criteria cannot always be met with laparoscopic surgery. With further refinements in instrumentation, robotic surgery, and laparoscopic ultrasonography, these goals may be achieved in the future. In some series, there is liberal use of pancreatic resection, as opposed to

enucleation; stapling the pancreas is a gross motor skill, easily carried out through a trocar. This, then, defies the edict of organ preservation in insulinoma surgery. When all the small series of laparoscopic insulinoma surgery are combined, certain characteristics emerge. Fistula rates are higher than in open surgery, perhaps twice as high in many series. Superficial tumors are better managed laparoscopically than deeper seated tumors, especially in the head and uncinate. Tumors in the body and tail are better managed laparoscopically than tumors elsewhere in the gland. Some authors advocate the endoscopic placement of a nasopancreatic catheter preoperatively in order to perform intraoperative pancreatography along with IOUS before and after enucleation to help detect pancreatic fistulas and guide resection [50]. The risks and benefits of this modality need further clarification. We need a multicenter trial among recognized experts that compares open to laparoscopic insulinoma surgery, looking not only at success and complications, but also cost and quality of life in a well-defined protocolized study with strict adherence to definitions, particularly as they relate to pancreatic-associated complications.

Patients requiring a gradient-guided pancreatectomy, such as those with an occult insulinoma in the body or tail or those with either diffuse or focal nesidioblastosis in the splenic artery distribution, may benefit most from laparoscopic distal pancreatectomy, with or without splenic preservation. There are two words of caution with regard to splenic preservation. Its importance in adults, unlike in children, is likely over-rated. Preservation of short gastric vessels alone may be tolerated, but may not maintain immunologic tolerance to encapsulated microorganisms. Such a strategy for larger spleens may lead to infarction and possible abscess formation. Splenic preservation on its principal blood supply, especially when performed laparoscopically, may increase ones risk for late splenic vein thrombosis, sinistral hypertension, and the long-term development of gastric varices.

When the splenic artery distribution alone is positive, a conservative distal pancreatectomy is performed to the left of the superior mesenteric vein. When the gastroduodenal artery or superior mesenteric artery distribution are also involved, we perform an extended distal pancreatectomy to the right of the superior mesenteric vein. Whipple procedures are only performed for severe cases of NIPHS, when two consecutive SACSTs are positive in the gastroduodenal artery and/or superior mesenteric artery distributions without a step up in the splenic artery distribution.

Results of Pancreatic Surgery for NIPHS

To date, approximately 40 patients have undergone pancreatic resection for NIPHS or postbariatric hypoglycemia. Symptomatic relief is almost universal at least in the short term. Three patients have experienced recurrence of milder forms of their original symptoms. The long-term prognosis is at present unknown as is the incidence of diabetes after pancreatic surgery. These considerations should be foremost when discussing surgical options in patients with relatively mild/infrequent symptoms (especially persistently obese patients after bariatric surgery), and it is uncertain that operative intervention is required.

Insulinomas and the MEN1 Pancreas

Insulinomas are the second most common functioning neuroendocrine tumor affecting the pancreas and duodenum (PDNET) in MEN1 patients, and the most common functioning PDNET syndrome in MEN1 patients under the age of 25. We now know from experience and SACST data that many of the insulin-producing tumors in MEN1 are unifocal. Recurrence rates are, however, the highest in MEN1 patients: over 20% in our series. Patients are best managed with an extended distal pancreatectomy and enucleation of residual tumors in the head and uncinate when technically feasible and safe [51–56].

Malignant Insulinomas

These are rare, often large tumors with regional and/or hepatic metastases at presentation. Treatment is with formal resection and

lymphadenectomy (pancreatoduodenectomy or distal pancreatectomy/splenectomy). Palliative resections can obviate the sequelae from uncontrolled hormonal production, even in the setting of hepatic metastases. Because of the indolent nature of this malignancy, multiple treatment modalities are available to palliate such patients including: hepatic metastasectomy and liver resection, hepatic arterial (chemo)embolization, radiofrequency ablation of liver and bone metastases, octreotide derivatives, diazoxide, and chemotherapy; most notably with streptozotocin doxorubicin, and 5-fluorouracil [57, 58].

Management of Intraoperative Complications

Ductal injury during enucleation of an insulinoma can have devastating consequences. IOUS can be helpful in guiding the enucleation or the decision to resect versus enucleate. Once enucleation is complete, intravenous secretin is given to look for major pancreatic duct disruption. This will also dilate the pancreatic duct and facilitate completion of intraoperative ultrasonography. Unfortunately, even when the main duct is intact, it may be hard to visualize in and around an enucleation site, again raising the potential role for completion nasopancreatic ductography. This awaits further clinical confirmation. Major duct injury in the body and tail mandates a distal resection. Such injuries in the pancreatic head are more problematic and have been managed with primary duct repair and stenting, drainage into a defunctionalized roux limb, and, least often, pancreatoduodenal resection.

Conclusion

Endogenous hyperinsulinemic hypoglycemia has many potential causes of which insulinoma is the most common. Optimal management first requires confirmation that hypoglycemia is indeed the cause of the patient's symptoms. Subsequently once the mechanism of hypoglycemia has been determined, appropriate efforts to localize and treat the source of hypoglycemia can be undertaken. Insulinomas are typically single, benign tumors that can safely be enucleated by an experienced surgeon. More extensive resection is usually indicated in MEN1 syndrome. Patients who experience hypoglycemia after bariatric surgery may benefit from a trial of medical therapy prior to gradient-guided pancreatic resection. Additional excellent review articles on insulinoma can be found in the enclosed references [59–63].

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38

Gastrinoma

Masayuki Imamura and Izumi Komoto

Introduction

In 1955, Zollinger and Ellison described two patients in whom jejunal peptic ulcers recurred, successively resistant to conventional ulcer operations including vagotomy and a few distal gastrectomies until a total gastrectomy was performed [1]. The first patient died of the disease. There was no doubt that these persistent peptic ulcers were caused by the extreme acid hypersecretion from a small remnant of stomach left after subtotal gastrectomy. In both of the patients, islet cell tumors were found in the body of the pancreas, and they were suspected of having a causative relationship with the extreme gastric acid hypersecretion. In 1960, Gregory and Tracy proved that gastrin was present in the extract of a pancreatic islet tumor in a patient with Zollinger–Ellison syndrome (ZES). They concluded that ZES is caused by hypergastrinemia due to existence of a gastrin-producing tumor; that is, a gastrinoma [2]. Initial attempts to manage ZES by surgically resecting pancreatic gastrinoma, including blind distal pancreatectomy, failed with a high rate of morbidity and mortality. Both an inadequate understanding of the clinicopathological features of gastrinoma and poor localization tools led to failure of resection surgery in the past. It deserves mention that despite those limitations, Oberhelman et al. had cured a few patients with ZES by performing pancreaticoduodenectomies for duodenal gastrinomas [3, 4].

Because of the high failure rate, the surgical treatment strategy for ZES evolved from attempted resection of the gastrinoma to total gastrectomy in order to eliminate the effect of gastric acid hypersecretion [5]. Subsequently, medical treatment, especially with proton pump inhibitors, had replaced surgical treatment by total gastrectomy [6, 7]. These therapies, although controlling the gastric acid secretion, were able to inhibit neither the growth nor the metastatic potential of the gastrinoma. In one reported series, about 30% of patients with ZES in whom hyperacidity had been medically well controlled died at a mean follow-up of 14 years and half of them died of tumor progression [8]. Hepatic metastases were the primary determinant prognostic factor. Once metastases developed, most of the patients died within 3 years [8, 9]. Development of a reliable preoperative localization method that guides the curative resection surgery for gastrinoma is essential before effective surgical procedures could be utilized.

With the introduction of the selective arterial secretagogue injection test (SASI test) and somatostatin receptor scintigraphy (SRS), strategies for the curative resection of gastrinoma in patients with ZES could be established [10–13]. With an increase in the number of curative resection surgeries, several important pathological characteristics of gastrinoma were elucidated [14, 15]. Our current understanding

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of ZES is a disease condition caused by a small gastrinoma less than 5 mm in diameter, which is located not only in the pancreas but even more frequently in the duodenum [14–17]. However, even the smallest gastrinomas may be associated with lymph node metastases. In patients with ZES and multiple endocrine neoplasia type 1 (MEN 1), gastrinomas develop primarily in the duodenum; two thirds of these are multiple and half are microscopically numerous. In addition, multiple, microscopically numerous, neuroendocrine tumors (NET) other than gastrinoma are usually found in the pancreas. These larger visible or palpable NETs are rarely gastrinomas in MEN 1 patients [16–21].

Diagnosis

Clinical Symptoms

Patients complain of symptoms caused by a long-lasting gastric acid hypersecretion; that is, gnawing abdominal pain, intermittent diarrhea, abdominal fullness, and heartburn at an early stage. Subsequently, abdominal colic, frequent vomiting, hematoemesis, persistent diarrhea, or melena may develop as originally described by Zollinger and Ellison [1]. At present, due to the early administration of proton pump inhibitors for patients with peptic ulcer, it has been rather difficult for a doctor to suspect ZES based on clinical symptoms alone [7, 8, 17]. Recently, regurgitation esophagitis has become one of the most typical diseases that are associated with ZES, as well as jejunal ulcer or multiple duodenal ulcers [17, 22]. The measurement of serum immunoreactive gastrin concentration (IRG) in patients with reflux esophagitis or long-lasting abdominal discomfort has become the most important step in establishing an early diagnosis of ZES (Table 38.1) [8, 22].

Table 38.1. Diagnosis of ZES

Clinical features
Regurgitation esophagitis
Persistent peptic diseases
Duodenal ulcers (multiple, recurrent, atypical)
Jejunal ulcer
Perforation
Bleeding
Persistent diarrhea
Hyperparathyroidism, pituitary tumor
Laboratory findings
Hypergastrinemia (>200 pg/ml, >80 pg/ml after distal gastrectomy)
Hypersecretion of gastric acid (BAO > 15 mEq/h, >5 mEq/h after distal gastrectomy)
24 h pH monitor (>70% holding time less than pH 4)
Hypercalcemia, other endocrine abnormality

Table 38.2. Differential diagnosis of ZES

A. Hypersecretion of gastric acid
Pyloric stenosis
Antral G-cell hyperplasia
Retained gastric antrum
Short bowel syndrome
Helicobacter pylori infection
B. Hypergastrinemia
Pernicious anemia
Chronic renal failure
Atrophic gastritis
H. pylori infection
Long antiacid therapy
Postvagotomy

Differential Diagnosis

Coexistence of hypergastrinemia and gastric acid hypersecretion is a pathological phenomenon that is never observed in normal persons. Demonstration of this phenomenon has been the golden standard for the diagnosis of gastrinoma, although there are a few diseases that show similar phenomenon as listed in Table 38.2. The range of the fasting IRG (FSG) in a normal person is less than 150 pg/ml, although in a person who underwent distal gastrectomy FSG it is less than 40 pg/ml. So, an increase of FSG beyond these ranges should indicate hypergastrinemia [7, 10]. Gastric acid hypersecretion is measured with either the gastric acid output analysis or the 24-h pH monitoring of the stomach.

The intravenous secretin injection test (secretin test) has been believed to be the most useful test for the differential diagnosis of ZES [23, 24]. However, it has been shown experimentally that not only gastrinoma cells but also normal G cells

release gastrin when directly stimulated by a pharmacological dose of secretin [25, 26]. It has been found clinically that the secretin test often becomes positive in a patient with atrophic gastritis, retained gastric antrum, or pyloric stenosis [13, 19]. Therefore, the diagnosis of ZES cannot be established with the secretin test only without considering other clinical aspects. Patients with a retained gastric antrum, pyloric stenosis, or antral G cell hyperplasia may also require surgery but not the type of procedures for ZES [13, 19].

There are other diseases which exhibit hypergastrinemia but not gastric acid hypersecretion, such as a prolonged administration of a proton pump inhibitor, chronic renal failure, and pernicious anemia. Differential diagnosis of these diseases is easily done with assessment of the extent of gastric acid secretion [12, 13, 17].

Localization

Conventional Imaging Techniques

Conventional imaging techniques have been proven to be insensitive for the preoperative localization of gastrinoma [27–29]. Visualization rate of gastrinomas by ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and arteriography has been reported as between 20 and 60% [25, 27–29]. They are useful for identifying hepatic metastases and gastrinoma larger than 2 cm in diameter, but they are not sensitive enough to identify tumors for curative resection [28, 29].

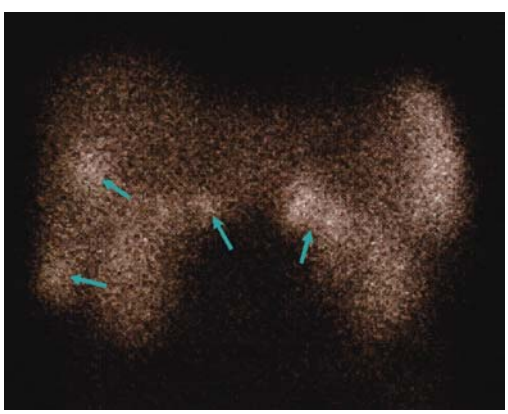

Fig. 38.1. SRS scintigram showing a hot spot in a patient with ZES. Laparotomy revealed an endocrine tumor 10 mm in diameter in the first portion of the duodenum, which was extirpated through a duodenotomy wound. The tumor was immunohistochemically diagnosed as a gastrinoma.

Specific Localization Tests

Development of the SASI test and SRS was innovative and helped to establish the standard strategy for curative surgery in patients with ZES [13, 17, 19, 21]. These techniques were developed by the basic science studies of the mechanism of hormone secretion in endocrine tumor cells (Figs. 38.1 and 38.2) [30–32].

SASI Test

The principle of the SASI test is to detect the feeding artery of the symptomatic NET and localize the tumor to the anatomical field supplied by the artery. The field of the diagnosed artery must be checked in each patient on the arteriogram [10]. The accuracy rate of the SASI test is more than 90% in both gastrinoma and insulinoma [10, 12, 33–37]. Briefly, a secretagogue is injected into the splenic artery (SPA), the gastroduodenal artery (GDA) and the superior mesenteric artery (SMA), and the hepatic venous blood (HV) samples are drawn before, and 20, 40, 60 s after the injection. The changes of hormone level of HV samples are measured and compared with the HV hormone level before the stimulation [10].

In patients with ZES, when the increase of the HV-IRG at either 20 or 40 s was more than 80 pg/ml and more than 20% from the basal IRG, the artery is determined to be a feeder of the gastrinoma. By seeing the blood flow field of the feeding artery on the arteriogram in each patient, the gastrinoma can be localized (Fig. 38.2A) [10].

More precise localization is possible by injecting the secretagogue into the peripheral branch of either the superior mesenteric or the GDA. When the SPA is the feeder, more precise localization is possible by injecting secratagogue at a different level in the SPA (Fig. 38.2B) [12]. Hepatic metastasis also can be diagnosed by taking the blood samples from both the right and the left hepatic vein after the injection of the secretagogue into the proper hepatic artery [10, 12].

Secretin (30U) was used for a long period as the secretagogue for gastrinoma. Now we prefer

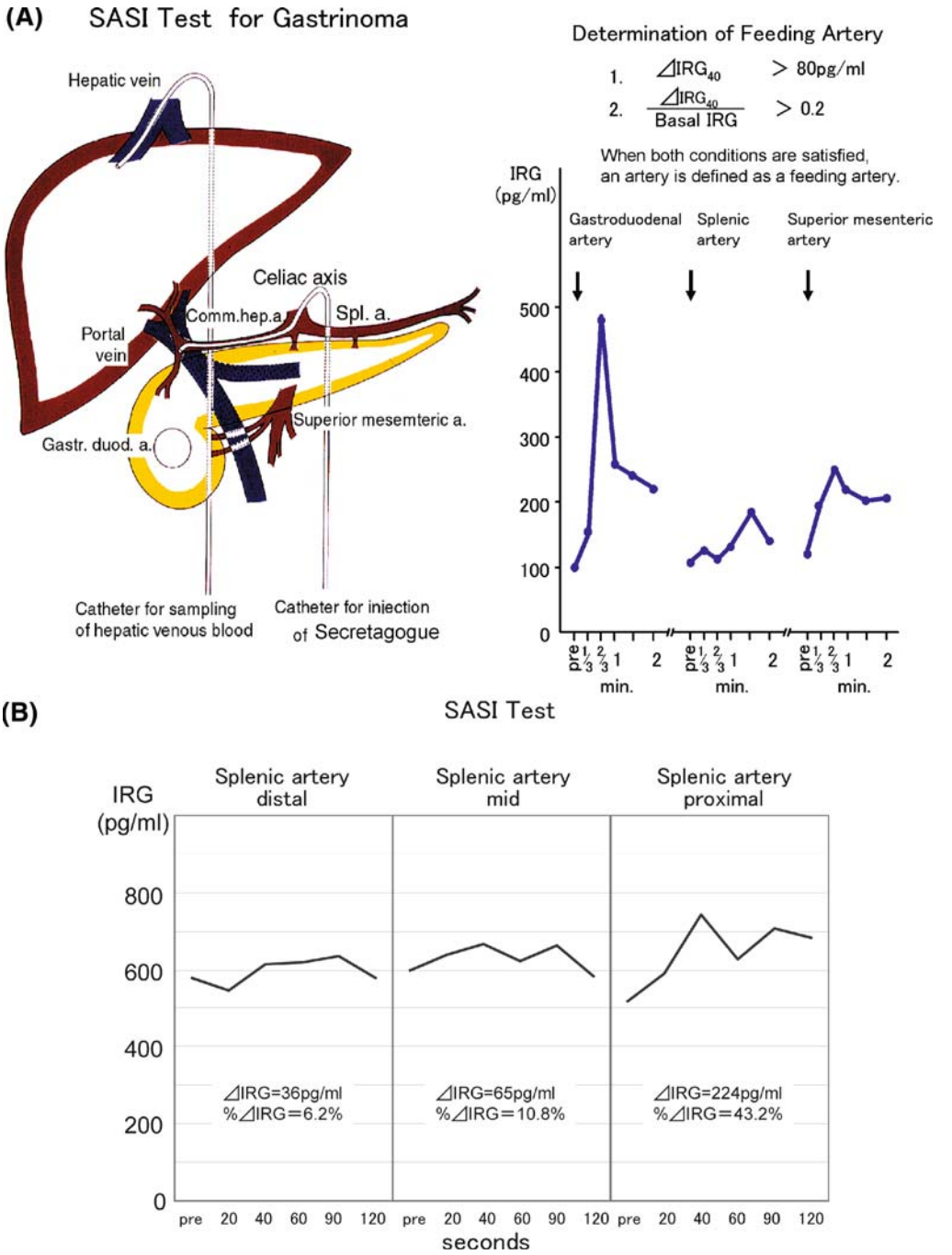

Fig. 38.2. (**A**) Schematic diagram of SASI test is shown on the *left* and the criteria for determination of the feeding artery of gastrinoma is shown on the *upper right*. The *lower right* graph shows the results of SASI test in a case. In this case, the gastroduodenal artery is a feeder of gastrinoma. (**B**) Results of super SASI test. The splenic artery (SPA) had been diagnosed as a feeding artery of gastrinoma and the superselective SASI test was performed by injecting secretin into three different points in the SPA. The test was positive only after the injection of secretin into the most proximal point of the SPA. Therefore, gastrinoma is diagnosed to be located in the feeding area of the greater pancreatic artery, that is, the body of the pancreas.

Table 38.3. Comparison of secretin with calcium in SASI test for eight patients with ZES

Calcium	
Positive	6
Negative	2
Secretin	
Positive	2
Negative	0

calcium gluconate solution (0.78 mEq of calcium), since secretin has become very expensive [12, 36, 37]. In most patients with ZES, calcium solution is useful. However, in about 20% of patients with ZES it is not useful and secretin should be used instead (Table 38.3) [21]. The SASI test with calcium solution is also useful for localization of NET other than gastrinoma, such as insulinoma, glucagonoma, and VIPoma [36–39] (Imamura, Personal experience).

Our experiences in localization of gastrinoma with the SASI test are as follows: in 32 patients with ZES, the SASI test successfully localized gastrinoma in 30 patients (93.8%) and in two patients secretin did not stimulate the gastrinoma. In 13 patients with MEN 1 and ZES, the SASI test successfully localized duodenal gastrinomas in the pancreatoduodenal region in all of them: GDA was positive in 9 patients, SMA was positive in 6 patients. In 14 patients with sporadic duodenal gastrinoma, the SASI test was useful. In 14 patients with pancreatic gastrinoma, 13 patients had liver metastases and only one patient was free of liver metastasis. The SASI test was useful for localizing pancreatic gastrinoma in eight patients and was useful for the curative resection of the pancreatic gastrinoma by pancreaticoduodenectomy (PD) in the one patient without liver metastases.

Based on the results of the SASI test, curative resection of gastrinoma can be safely performed. However, the SASI test cannot predict how many gastrinomas exist in the localized field. Gastrinoma is often multiple, and has high metastatic potential to the regional lymph nodes. Thus, there are two options for the surgeons performing curative resection surgery for gastrinoma based on the localization by the SASI test: One is to perform an en bloc resection, such as PD or pylorus-preserving pancreaticoduodenectomy (PPPD) or distal pancreatectomy. The other is to enucleate all the gastrinomas in the field the SASI test localized. In the latter case, there is likely to be a higher rate of leaving gastrinoma or metastatic lymph nodes of the abdomen compared with an en bloc resection. In order to prevent an incomplete resection, the intraoperative secretin test (IOS) using a rapid radioimmunoassay of serum IRG is useful [40].

Somatostatin Receptor Scintigraphy

The principle of SRS is to visualize NETs that have somatostatin receptors on the cell membrane on the scintigram by injecting radiolabeled somatostatin analogue intravenously [33]. Most NETs have somatostatin receptors. SRS easily visualizes most NETs larger than 2 cm anywhere in the body (Fig. 38.1) [11, 17, 41]. The sensitivity of SRS depends on the size of NET. It has been reported that sensitivity is as high as 96% for NETs larger than 2 cm, but only 30% for NETs smaller than 1 cm [17, 41]. SRS cannot differentiate gastrinoma from other coexisting NETs. Therefore, the SASI test should be used to localize gastrinomas.

Intraoperative Techniques

Intraoperative US (IOUS) is very useful for the identification of small pancreatic gastrinomas while intraoperative duodenoscopy is also useful for detecting duodenal gastrinoma [12, 13, 17, 20]. It had been suggested that the entire pancreas should be exposed when searching for gastrinoma. However, since the development of the SASI test, preparation of the field that the SASI test localized is sufficient for both identification and resection of the gastrinoma [10, 12, 34–35, 42, 43].

Duodenal gastrinoma larger than 5 mm can be detected by palpating the tumor in the duodenal wall between thumb and index finger. Smaller ones cannot be identified without using the duodenoscopy or by careful finger palpation of the duodenal mucosal membrane through a duodenotomy wound [15, 21]. Any duodenal tumors resected should be intraoperatively sent to a pathologist for a rapid confirmation of endocrine tumor.

The IOS test is recommended for confirming the curability of the resection surgery, before closing the abdomen. As in the usual secretin test, two units per kilogram of body weight is injected via the peripheral vein and venous blood samples are drawn before, and 2, 4, and 6 min after the injection [41].

Surgical Treatment

Curative resection surgery can be performed for most patients with gastrinomas. Long-term medical treatment that had successfully replaced total gastrectomy for controlling the gastric acid hypersecretion in patients with gastrinoma is now indicated only for patients with inoperable gastrinomas due to distant metastases or other reasons (Fig. 38.3) [19, 21].

With an increase in the number of tumor resection cases, several important pathological characteristics of gastrinoma have been elucidated. These have contributed to the decision making with regard to the modes of resection surgery.

Surgery and Pathological Characteristics of Gastrinoma

1. Since 1955, sporadic gastrinoma has been thought to arise mostly in the pancreas, but we now know that they actually arise more frequently in the duodenum [16–22]. They are usually single and rarely associated with pancreatic gastrinoma. The incidence of lymph node metastases in sporadic gastrinoma of either the duodenum or the pancreas has been reported to be more than 60% [16–22]. The incidence of hepatic metastases is less than 10% in duodenal gastrinoma but is almost 60% in pancreatic gastrinoma [22]. The size of gastrinoma is not correlated with the metastatic potential [16–20]. All gastrinoma should be treated as malignant [21–29, 36].
2. Gastrinoma associated with MEN 1 arise mostly in the duodenum [16–21]. Two thirds of them are multiple and a half of them are numerous [12]. Some surgeons have recommended that resection surgery is not indicated for the duodenal gastrinoma in MEN 1 patients [30, 42–43]. They report that 30% of the patients have more than 20 duodenal tumors, and 86% of patients have positive lymph node metastases [30, 42–43]. They believe that invasive surgery like PD or PPPD is highly unlikely to cure but is too risky and that their prognosis remains good without operation [17, 42–43]. However, hepatic metastases will eventually develop in more than 10% of patients and life-long administration of anti-acid medication is necessary [30]. Currently, curative resection of duodenal gastrinomas in patients with MEN 1 patients can be accomplished with little or no morbidity by pancreas-preserving

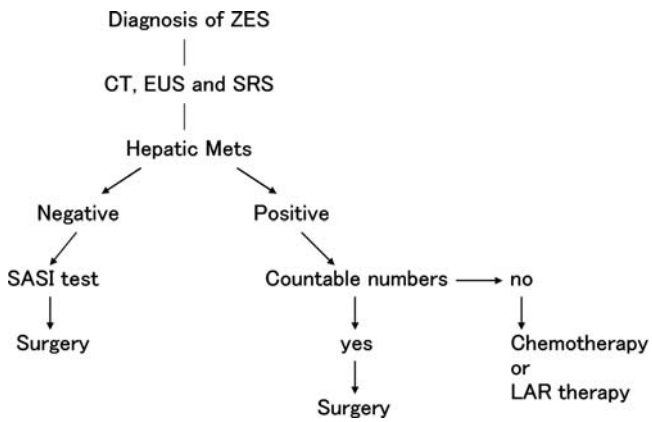

Fig. 38.3. Treatment strategy for gastrinoma.

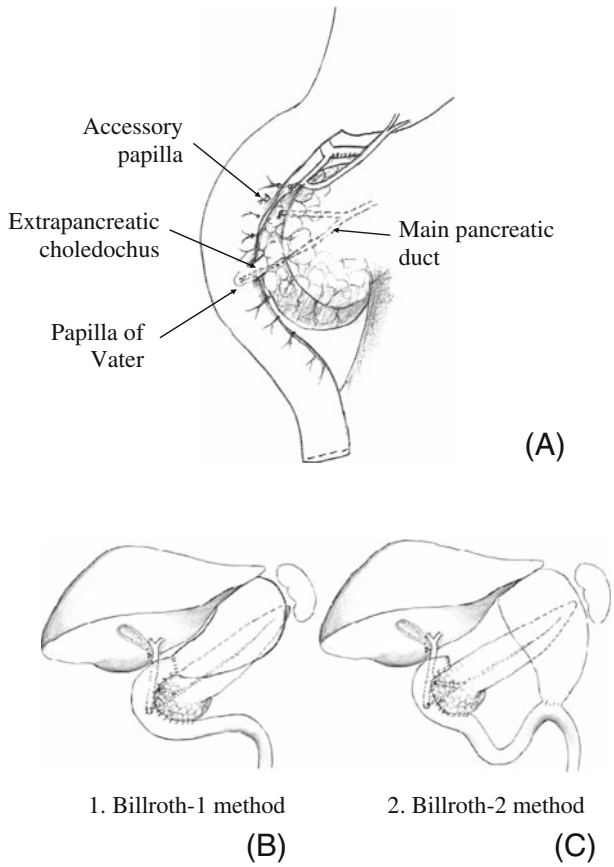

Fig. 38.4. Schematic diagram showing PPTD. The duodenum is totally resected from the head of the pancreas by cutting the duodenal branches of the pancreatico-duodenal arcades. The accessory pancreatic duct is ligated and cut. The structure of the major papilla is saved by stripping only the mucosal layer from the muscular layer of the major papilla. After the incisional papillotomy, the opened papilla is anastomosed to the small incision of the jejunum for reconstruction of the biliopancreatic internal drainage. Reconstruction of the alimentary tract is performed with either Billorth 1 or 2.

total duodenectomy (PPTD) in which the entire pancreas is preserved, in contrast to the more invasive PD or PPPD (Fig. 38.4) [22, 44].

3. Another problem in MEN 1 patients is how to treat multiple gross and microscopical NETs in their pancreas [21, 42]. There have been controversies regarding the treatment strategy for them. In one report, 57 patients with MEN 1 and pancreatic NETs were followed until the pancreatic NETs grew to 2.5 or 3 cm in diameter [45]. Hepatic metastases developed in 13 patients (23%) during an observation period of 8 years, and three of them died of the disease [30]. Now, a more aggressive resection operation is indicated for pancreatic NETs larger than 1 cm in diameter [20–22].
4. Ectopic gastrinoma may be located not only in a lymph node, but the stomach, liver, gallbladder, ovary, and even in the lung or the heart [46–51]. SRS has been the best means for identification of these rare ectopic gastrinomas [46–51].
5. A small number of hepatic metastases is often cured by surgical treatment by resecting both the liver tumors and the primary gastrinoma [52–56]. Reoperation and cytoreductive surgery are also recommended for palliating hypergastrinemia and potentially prolonging patient survival [54–56].

Table 38.4. Surgery for patients with MEN1 and ZES

				Gastrinoma			Surgery		Metastasis				
No.	Age (y.o.)	Gender	ZES	Location	Number	Size (mm)	Modus	Year	N	L	Pancreas NET	Other glands	Prognosis
1	39	F	+	D	7	3–5	PD,ParX	1991	1	0	6	Par	DOD(4y)
2	44	M	+	D	1	10	PD	1991	1	0	5	Pit, Par	Alive
							GasX	1984					
3	49	M	+	D	7	2–4	Dx	1997	0	0	Px (1)	Par	Alive
							ParX	1997			Glucagonoma		
							ParX	1984				Par	Alive
4	61	F	+	D	5	2–4	Dx	1995	0	0	2		
				D	1	4	Dx	2004	0	0			
5	21	M	+	D	1	10	PD	1997 (Aug)	0	0	0	Pit	Alive
							PitX	1997 (Oct)					
6	62	M	+	D	Mult	2–6	DP	1999	0	0	1	Par	Alive
							ParX	2002					
							ParX	1999				Par	Alive
7	56	F	+	D	3	1–1.8	Dx	2001	1	0	Px (3)		
				D	2	1–3	Dx	2007					
8	44	F	–	–	–	–	PPPD	1994	0	0	1 (40 mm)		Alive
			+	D	1	9	ParX	2001 (Jan)	2	0	0	Par	
							Dx	2001 (Apr)					
9	33	M	+	D	1	10	ParX	2001	1	0	Mult	Par	Alive
							Dx, DP	2003					
10	51	F	+	D	Numerous	1–4	ParX	2003 (Apr)	1	0	1	Par	Alive
							PPTD, Px	2003 (Nov)					
11	30	M	+	D	1, BrunnH	5	ParX	2004 (Apr)	0	0	1	ParPit	Alive
							PPTD	2004 (Jul)					

Table 38.4. (continued)

				Gastrinoma			Surgery		Metastasis				
No.	Age (y.o.)	Gender	ZES	Location	Number	Size (mm)	Modus	Year	N	L	Pancreas NET	Other glands	Prognosis
12	33	M	+	D	1, BrunnH	5	ParX	2003	0	0	Mult	Par	Alive
							PPTD, DP	2004					
13	48	F	+	D	Numerous	1–5	PPTD	2007 (Apr)	1	0	Mult	Par	Alive
							ParX	2007 (Sep)					

M: male; F: female; ZES: Zollinger–Ellison syndrome; NET: neuroendocrine tumor; Par: hyperparathyroidism; ParX: parathyroidectomy; Dx: extirpation of duodenal gastrinoma; GasX: distal gastrectomy; PD: pancreatoduodenectomy; PPPD: pylorus-preserving pancreatoduodenectomy; PPTD: pancreas-preserving total duodenectomy; DP: distal pancreatectomy; Pit: pituitary tumor; PitX: resection of pituitary tumor; mult: multiple; BrunnH: Brunner gland hyperplasia; DOD: dead of other disease.

Surgery for Sporadic Gastrinoma

Pancreatic Gastrinoma

Most pancreatic gastrinoma have been detected after they have grown larger than 2 cm in diameter. Two thirds of them have had hepatic metastases. They are all considered to be potentially malignant [9, 12–13, 22]. Thus, early diagnosis and early resection surgery is recommended. Early diagnosis of ZES may have become more difficult since the common use of proton pump inhibitors for patients with peptic disease symptoms [20, 22]. Patients with ZES have often delayed in diagnosis for many years. Early check of the serum gastrin concentration in patients with a long history of upper abdominal discomfort should be widely done [15, 20].

A pancreatic resection surgery for gastrinoma should be similar to surgery for pancreatic ductal cancer, such as PD or PPPD or distal pancreatectomy with dissection of regional lymph nodes [22, 57–58]. For the pancreatic microgastrinoma less than 5 mm in diameter, less-invasive surgery such as an enucleation and lymph node dissection might be indicated.

Duodenal Gastrinoma

Recently, sporadic duodenal gastrinomas are more frequently detected than pancreatic gastrinomas [17, 22, 43]. Most sporadic duodenal gastrinomas are single and less than 1 cm in diameter, although more than 60% of them are associated with lymph node metastases [21–22].

Extirpation of the submucosal duodenal tumor and an aggressive dissection of the regional lymph nodes is indicated [21]. Rarely, a pancreatic gastrinoma or other duodenal or pancreatic NET coexists with a duodenal gastrinoma [22]. It is important therefore to examine the head of the pancreas carefully before searching for a duodenal tumor. These patients with multiple NET should always be reevaluated for possible MENI syndrome.

Intraoperative duodenoscopy is useful for identification of a submucosal duodenal tumor [22, 42]. All of the resected tumors should be sent for a rapid pathological diagnosis for confirmation that it is an endocrine tumor because there are a variety of submucosal nodules in the duodenum, such as ectopic pancreas, hyperplasia of the Brunner's gland, and ulcer scars that may mimic a small gastrinoma [22].

Surgery for Gastrinoma in MEN 1

In patients with MEN 1, hyperparathyroidism develops in 95–100%, pituitary adenoma in 20–100%, and pancreatic NETs arise in 80–100% [12, 17, 21]. In most patients with MEN 1 and ZES, hyperparathyroidism coexists with hypergastrinemia. Resection of gastrinoma and parathyroid can be performed simultaneously or sequentially. When the complications caused by gastric acid hypersecretion are severe, we recommend performing parathyroidectomy first. Normalization of serum calcium level results in decreased gastric acid secretion and contributes to the healing of the complications [59].

There have been controversies regarding the treatment strategy for duodenal gastrinomas and pancreatic NETs in patients with MEN 1 [12, 17, 21, 45], but recently, a consensus has been reached based on clinical studies [21, 45].

Duodenal Gastrinoma in MEN 1

In patients with MEN 1, gastrinomas arise primarily in the duodenum [16–17, 20–22]. They are also potentially malignant and highly metastatic to the regional lymph node, although the rate of hepatic metastases is less than 10% [16, 20–22]. The SASI test is useful to confirm not only the presence of the gastrinoma in the pancreatoduodenal region, but also the absence of a concomitant gastrinoma in the body or tail of the pancreas [22].

There have been controversies regarding the modes of surgical resection for duodenal gastrinomas in MEN 1 patients. For those who performed only conservative surgery, such as enucleation or partial resection of the duodenum for duodenal gastrinomas, a high rate of

recurrence of hypergastrinemia has been reported. More aggressive resection surgeries such as PD or PPPD were avoided because of a potential high rate of morbidity and mortality [45]. On the other hand, for those who have done PD or PPPD for potentially malignant duodenal gastrinomas [12, 57–58, 69–70], most have reported a higher cure rate with no mortality and a lower rate of morbidity [57–58, 69–70]. Few surgeons have proposed a total pancreatectomy because of the potential difficulties in management of the postoperative hyperglycemic status.

We have reported a high cure rate of hypergastrinemia after PPTD for multiple or numerous duodenal gastrinomas [22, 44]. In PPTD, the entire pancreas is preserved as well as the main pancreatic duct. No anastomosis between the main pancreatic duct and the jejunum is necessary [44]. Thus, anastomotic pancreatic leakage does not occur (Fig. 38.4). PPTD is less-invasive operation compared with PD, and postoperative complications did not result in our four patients (Table 38.4) [22]. They have maintained normal serum gastrin levels and negative secretin test for an observation term ranging between 4 years and 6 months, postoperatively. Lymph node dissection should be aggressive, and sometimes should include dissection of the paraaortic lymph nodes close to the posterior surface of the pancreas head, because recurrence from metastatic lymph nodes is not rare [22].

Of course, there may be some patients in whom only the resection of either the upper part or the lower part of the duodenum is sufficient for the cure of duodenal gastrinoma. An adequate procedure should be chosen on the basis of the distribution of the duodenal gastrinomas and numbers of the duodenal microgastrinoma in order to prevent the recurrence of ZES [22].

Our experiences of resection surgery for 13 patients with MEN 1 and ZES are shown in Table 38.4. Eight patients had multiple duodenal gastrinomas, and six of them had seven or more duodenal gastrinomas. In five patients who had single duodenal gastrinoma, one patient had microgastrinoma in Brunner glands in the duodenum. No patient had a pancreatic gastrinoma in the body or tail of the pancreas. Results of the SASI test were correct in all patients. Extirpation of duodenal gastrinoma was performed in five patients, PD in three patients, and PPTD in four patients (Fig. 38.5A–C). One patient (#8) underwent a parathyroidectomy and did not receive resection surgery for duodenal gastrinoma after the parathyroidectomy. He was transferred to our hospital due to an uncontrollable severe anastomotic jejunal fistula with sepsis following a distal pancreatectomy and subtotal

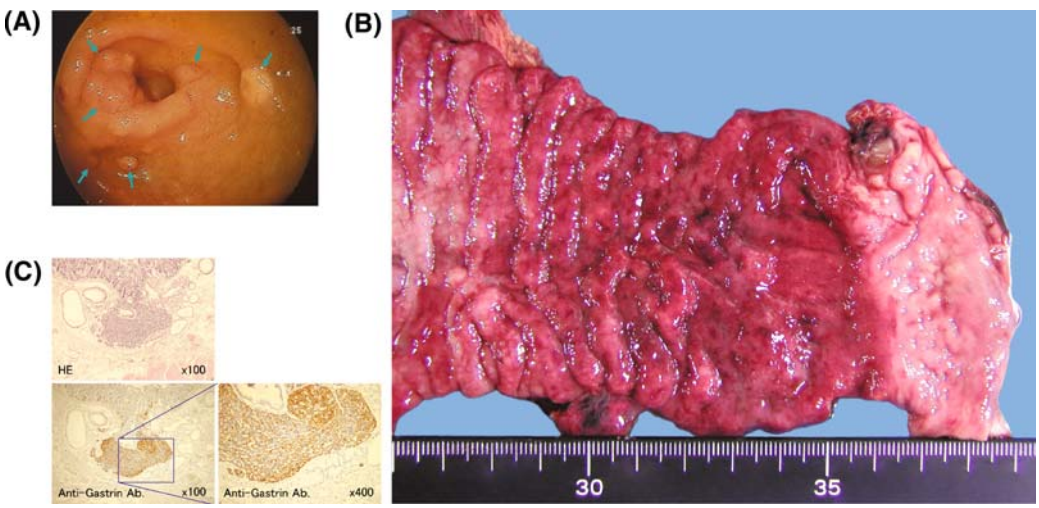

Fig. 38.5. (**A**) An example of the intraoperative duodenoscopy in a patient with MEN-1 and ZES. Note the multiple small submucosal duodenal tumors. (**B**) In the duodenal specimen after the PPTD, numerous small submucosal tumors are seen as well as ulcer scars. (**C**) Microscopic photo showing multiple submucosal tumors confirmed to be microgastrinomas by immunohistochemical staining with an antigastrin antibody.

gastrectomy for ZES at another hospital. We performed a parathyroidectomy first for the control of hypercalcemia. Subsequently, his hypersecretion of gastric acid subsided and the jejunal fistula healed. He has refused resection of duodenal gastrinoma since then [21].

Two patients who received partial duodenectomy recurred and received a second extirpation of duodenal gastrinomas, 6 and 9 years after the initial surgery, respectively. One patient (#8) who had undergone PPPD for a large nonsymptomatic NET in the head of the pancreas developed ZES 7 years after the PPPD. She was shown to have a duodenal gastrinoma with a gastroduodenal barium study and then underwent a resection of the residual duodenum. So far, only one patient died of other disease, but all other patients, including those who underwent the second operations, have been cured of hypergastrinemia during a follow-up period ranging between 6 months and 16 years.

Pancreatic Neuroendocrine Tumors in MEN 1

Patients with MEN 1 commonly have multiple and numerous microscopical NETs in the pancreas [21–22, 30, 42]. These NETs are usually asymptomatic. Some may be insulinomas, glucagonomas, somatostatinomas, PPomas, etc., but rarely gastrinoma. Some of them may metastasize to the liver at an early stage, but others take considerable time to do so. An extensive genetic analysis for differentiation of the highly metastatic NETs has been done, but thus far no established markers have been discovered [60–62]. Recent consensus for treating these pancreatic NETs is that earlier operations should be done whenever a pancreatic NET shows rapid growth or enlarges to more than 1 cm in diameter [21, 22].

Surgery for Ectopic Gastrinoma

Successful surgical resection for ectopic gastrinomas localized by SRS have been reported [47–52]. SRS should be done in any case of suspected ectopic gastrinoma [46–51]. Resection should include an adequate wide margin as well as the dissection of lymph nodes and can result in the resolution of ZES.

Laparoscopic Surgery for Gastrinoma

Some experts of laparoscopic surgery (LS) have reported successful experience in either enucleation or distal pancreatectomy for pancreatic NETs, mostly for insulinoma [52–64]. Further, they have reported that the complication rate after LS is not significantly different from that of open surgery. The rate of pancreatic leak was 10–40%. LS might be beneficial for some patients because it reduces the size of incision and shortens hospital stay. On the other hand, LS may sometimes cause severe complications that would have never taken place with open surgery.

Gastrinomas are often metastatic and multiple. An aggressive procedure often includes resection of the duodenum. Thus, it is agreed that laparoscopic resection for gastrinoma is not recommended [64].

In general, application of LS for pancreatic endocrine tumors varies and enucleation or simple distal pancreatectomy for benign tumors is the most common indication. Endocrine surgeons are reluctant to apply LS to this field because of the excellent results they could have achieved in conventional operations and the concern about the potential risks to the patients when LS is performed by inexperienced surgeons. A registry system should be established to record the results of LS for endocrine tumors as well as to maintain the results under general surveillance [65].

Chemotherapy and Somatostatin Analogue

Chemotherapy and somatostatin analogue (octreotide) therapy have been used for either prolongation or improvement of the quality of life in patients with inoperable metastases from NET. Streptozotocine (STZ) and fluorouracil (5-FU) or cisplatin (CDDP) with etoposide have been shown to be very useful in some reports,

but in general the response rate of gastrinoma to chemotherapy is rather low. Recently, octreotide therapy has become more readily available for patients with NET. Development of long-acting repeatable octreotide (LAR) therapy has enabled octreotide therapy to be administered by one monthly intramuscular injection. As almost all gastrinoma cells have somatostatin receptors, LAR therapy is useful for controlling hypergastrinemia and tumor growth in patients with ZES [66].

The proliferation index (PI) that is calculated based on the number of immunohistochemically positively stained cells for Ki-67 (MIB 1) antibody is an important indication of chemotherapy or LAR therapy. In addition, PI is also used for classification of pancreatic NET by the World Health Organization (WHO). Patients with well-differentiated NETs in which PI is less than 2% are considered to be good candidates for LAR therapy. On the other hand, patients with poorly differentiated NETs in which the PI is more than 15% are good candidates for chemotherapy. Medical treatment strategy based on PI value has just begun. It will take a few more years before the routine application of this strategy is justified [66–68].

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39

Rare Functioning Pancreatic Endocrine Tumors

Gerard M. Doherty and Senthil Jayarajan

Introduction

Pancreatic functioning endocrine tumors are a discrete assortment of neuroendocrine tumors arising from the islet cells of Langerhans and other secretory cells of the pancreas, each with its own distinct mode of presentation based on the moiety that is hypersecreted. They are generally indolent, slow-growing neoplasms with similar modes of diagnosis and treatment. After diagnosis and with appropriate management, they have potential for long-term survival of the patient.

This chapter will discuss the clinical presentation, diagnosis, and management of the rare pancreatic functioning tumors, namely glucagonomas, VIPomas, somatostatinomas, and others. It will not cover gastrinomas and insulinomas, as they have been covered in other chapters. Table 39.1 summarizes the clinical features of each of the tumors.

Glucagonoma

Glucagonomas are rare tumors of the α-islet cells of the pancreas that secrete various derivatives like glucagon and other peptides from the molecule preproglucagon. The glucagonoma syndrome was first described in 1942 and encompasses a characteristic migratory erythematous rash, anemia, mild diabetes mellitus, and in later stages, cachexia. It is alternatively referred to as diabetico-dermatogenic, diabetes-dermatitis, and catabolic syndrome. It has also been called the 4-D syndrome, which stands for dermatosis, diabetes, deep vein thrombosis, and depression.

Glucagon is a 29-amino acid polypeptide whose primary function is to maintain blood glucose levels by causing glycogenolysis in the liver and release of glucose into the bloodstream. Thus, it opposes the actions of insulin and prevents hypoglycemia. It also increases urea production through protein catabolism as well as the release of fatty acids and ketones into the bloodstream.

Epidemiology

Symptomatic glucagonomas are rare entities with an estimated annual incidence of 1 in 20 million, of which 60% are sporadic and the remainder as a part of the multiple endocrine neoplasia (MEN)-1 syndrome. There is an equal incidence among men and women. At the time of diagnosis, most tumors are greater than 5 cm in diameter with 60–80% chance of malignancy. Most are found to be metastatic (90%). Metastases occur primarily in the liver and the peripancreatic lymph nodes [1–3].

Clinical Features and Investigation

Glucagonomas present with the glucagonoma syndrome in about 57% of all reported cases [4]. According to the largest reported single

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Table 39.1. Characteristics of rare pancreatic functioning tumors

	Incidence (per million)	Activating hormone	Syndrome	Diagnosis	Malignant at diagnosis (%)
VIPoma	0.1	Vasoactive intestinal peptide (VIP)	Watery diarrhea, hypokalemia, hypochlorhydria	Elevated fasting plasma VIP	>60
Glucagonoma	0.05	Glucagon	Necrolytic migratory erythema, hypotension, hypokalemia	Elevated fasting plasma glucagon	>70
Somatostatinoma	0.03	Somatostatin	Diabetes, cholelithiasis, steatorrhea	Elevated fasting plasma somatostatin	>70
PTHrPoma		Parathyroid-related Peptide (PTHrP)	Hypercalcemia, bone pain	Serum Ca > 11 mg/dl Serum PTH undetectable, Elevated serum PTHrP	>99
ACTHoma CRFoma		Cortisol	Cushing's syndrome	24-hour urinary free cortisol > 100 μg, Plasma ACTH >50 pg/ml, No dexamethasone suppression No CRH suppression	>99
GRFoma		Growth hormone	Acromegaly	Elevated fasting plasma GRF concentration	>50
Neurotensinoma		Neurotensinoma	Tachycardia, hypotension, hypokalemia	Elevated fasting plasma neurotensin	>80

institution experience at Mayo Clinic, 21 patients with glucagonoma syndrome from 1975 to 1991 presented with cachexia (71%), necrolytic malignant erythema (67%), diabetes mellitus (38%), diarrhea (29%), and cheilosis or stomatitis (29%) [3]. Other symptoms associated with this syndrome include normocytic normochromic or macrocytic anemia, history of venous thrombosis, psychiatric disturbance, and neurological symptoms like ataxia, fecal, or urinary incontinence, and visual disturbances [2].

Necrolytic malignant erythema is the pathognomonic symptom of glucagonomas and is thought to be due to the hypoaminoacidemia caused indirectly by high levels of glucagon. It is a cyclic rash with a characteristic distribution centering in the perioral and perigenital regions and migrates centrifugally to the distal extremities. The lesions initially begin as erythematous patches that blister, which centrally breakdown and heal after 1–2 weeks, leading to postinflammatory central hyperpigmentation and peripheral crusting. Recurrence at other sites is common [2, 5]. It is important to note that necrolytic malignant erythema can occur in the absence of glucagonomas [6]. Zinc and fatty acid supplements are not effective in the treatment of the rash. The rash appears to clear with amino acid hyperalimentation [7].

Most patients develop glucose intolerance. The diabetes is normally mild and controlled effectively with oral hypoglycemic treatment. However, insulin therapy may be required. The complications of diabetes mellitus have not been reported with glucagonomas.

Weight loss may be attributed to the fact that glucagon is a major catabolic hormone. The cause of the normocytic or macrocytic anemia is

unknown and its severity has been related to the severity of the glucagonoma syndrome. Occurrence of thrombotic events has been appreciated in nearly 30% of patients and can be fatal. Depression is also a common presenting symptom [1–3].

Patients normally present with a combination of the rash, diabetes mellitus, and weight loss. With a positive clinical presentation and localization of the tumor, glucagonomas may be confirmed with a fasting blood glucagon level greater than 50 pmol/l.

Vasoactive Intestinal Polypeptide-Secreting Tumor

Vasoactive intestinal polypeptide-secreting tumors or VIPomas were first characterized in 1958 by Verner and Morrison [8]. The classic triad of secretory diarrhea, achlorhydria (or metabolic acidosis), and hypokalemia forms the clinical syndrome, sometimes referred to as the watery diarrhea syndrome. This syndrome has also been called the WDHA (watery diarrhea, hypokalemia, and achlorhydria) syndrome, the Verner–Morrison syndrome, pancreatic cholera, and endocrine cholera.

Vasoactive intestinal polypeptide (VIP) is a 28-amino acid polypeptide that acts as a neurotransmitter in enteric neurons as well as those of the central nervous system, lungs, and other endocrine organs. Some of the biological effects attributed to VIP are induction of enteric smooth muscle relaxation, increased secretion of water by exocrine pancreas and intestine, decreased gastric acid secretion and absorption from the intestinal lumen, and modulation of immune function and pancreatic blood flow.

Epidemiology

The annual incidence of VIPomas is estimated to be around 0.1 per million in the general population [9]. Females are noted to be affected more often than males and the age of patients ranges from 32 to 75 years with a mean age of 49 years [10]. Most VIPomas are present in the pancreas (80%) with the most likely location being the tail of the pancreas. Approximately 50–70% are found to be metastatic at time of diagnosis with hepatic metastases most common [11, 12].

Clinical Features and Investigation

Chronic large volume secretory diarrhea is the principal symptom. Secretory diarrhea is characterized by diarrhea that persists during fasting periods with the stool isotonic to plasma, and the stool electrolytes accounting for all of the osmolality. Prolonged secretory diarrhea causes loss of water, potassium, and bicarbonate, which results in dehydration, hypokalemia, and acidosis.

Achlorhydria or hypochlorhydria, although part of the classic triad, is less common and is present in about 50% of patients. Hypercalcemia with normal parathyroid hormone (PTH) levels have also been noted in about half of the cases and is possibly due to increased bone resorption caused by VIP. Hyperglycemia is also noted and is attributable to the glycogenolytic effects of VIP. Flushing of face and upper chest can also be observed in about 20% of patients and is characterized by a patchy erythematous rash [11–13].

Diagnosis is based upon the clinical presentation of the patient, elevated VIP levels, and localization of the tumors. Secretory diarrhea, which may be intermittent at onset, and hypokalemia are present nearly all the time. Volumes less than 700 ml per day exclude diagnosis, while most patients present with volumes greater than 3 l per day. Elevated plasma VIP levels confirm the diagnosis and levels greater than 60 pmol/l are diagnostic. At the time of diagnosis, most tumors are greater than 3 cm in size, making visualization via CT or MRI feasible (see Fig. 39.1) [10, 13].

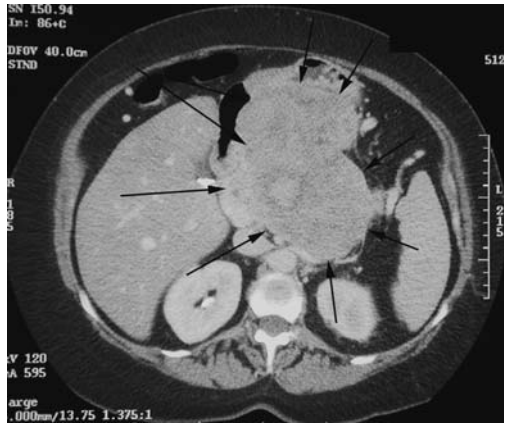

Fig. 39.1. CT scan for evaluation of pancreatic primary. This patient had a large VIPoma arising in the midportion of the pancreatic body, and producing both local compressive symptoms, and the WDHA syndrome. The *arrows outline* the tumor extent.

Somatostatinoma

Tumors that secrete excessive amounts of somatostatin, causing a syndrome characterized by steatorrhea, diabetes mellitus, hypochlorhydria, and cholelithiasis, are known as somatostatinomas. The first cases of somatostatinomas were reported separately in 1977 by Larsson [14] and Ganda [15].

Somatostatin is a cyclic tetradecapeptide and has two active forms, a 14- and a 28-amino acid hormonal derivatives from the same preprohormone. It is secreted in the gastrointestinal system including the intestine, stomach, and δ cells of the pancreas as well as the lung, brain, and adrenal tissues. It acts by inhibiting the release of peptide hormones like growth hormone, thyroid-stimulating hormone (TSH), gastrin, secretin, insulin, glucagon, and others. It also slows the rate of gastric emptying and reduces intestinal blood flow and smooth muscle contractions.

Epidemiology

Somatostatinomas are very rare with an estimated incidence of 1 in 40 million [16]. There is an equal sex distribution over all somatostatinomas, but among pancreatic somatostatinomas, there is a slight female preponderance (67%). The median age at diagnosis is 51 years with an age range of 26–84 years [17]. About 68% of the tumors originate from pancreas, of which 75% are present in the head of the pancreas [18]. Metastases are present in 77% of patients at diagnosis. The liver is the most common site (42%) of metastasis, followed by the lymph nodes (39%) [17].

Clinical Features and Investigation

The classic constellation caused by somatostatinomas demonstrates the inhibitory actions of somatostatin. Diabetes mellitus found in 95% of patients is caused by the suppression of the release of insulin. Cholelithiasis occurs with a frequency of 94% in patients. It is caused by the inhibition of cholecystokinin release and decreased gallbladder contractility. Less common presenting symptoms are steatorrhea (83%) and hypochlorhydria (86%). Steatorrhea and diarrhea may be caused by inhibited release of pancreatic enzymes, bicarbonate, and intestinal absorption, while hypochlorhydria is a result of the suppression of gastrin [19]. Significant weight loss over several months has been noted and maybe due to diarrhea and malabsorption. Hypoglycemia may be a result of inhibition of glucagon.

Diagnosis of somatostatinomas is often accidental, either during abdominal imaging or an abdominal procedure like cholecystectomy or exploratory laparotomy for suspected insulinomas or adrenal tumor. CT or MRI is often utilized to localize the tumor, which is often greater than 5 cm in diameter at diagnosis. Identification is achieved by the positive clinical picture and measurement of fasting somatostatin level. Levels greater than 14 mmol/l confirms diagnosis. A few patients with normal levels may be considered as having a false-positive result. Tolbutamide may be used to instigate secretion in these patients, which is not seen in normal subjects [7].

Other Rare Pancreatic Endocrine Tumors

ACTHoma

These tumors secrete excess amounts of either adrenocorticotrophin hormone (ACTH) or corticotrophin-releasing hormone (CRH). They create a classic Cushing's syndrome, which includes rapid weight gain, central obesity, proximal weakness, hirsutism, telangiectasia, hyperhidrosis, and thinning of skin causing easy bruising and red or purple striae. Biochemical investigation should reveal 24-hour urinary free cortisol ($>$100 μg/ml) and plasma ACTH ($>$50 pg/ml). Diagnosis is confirmed by the failure of suppression of cortisol levels with dexamethasone administration [20].

PTHrPoma

Hypercalcemia and its complications may be explained by skeletal metastases in the setting of a pancreatic mass, but bone is an uncommon site for isolated metastasis for pancreatic adenocarcinoma. Further investigation is, thus, obligatory, especially when conventional treatments are ineffective, since this could be

an indication of PTH-related protein (PTHrP) hypersecretion.

Clinical presentation is similar to hyperparathyroidism with bone abnormalities, nephrolithiasis, peptic ulcer, neurological and psychiatric complaints. However, PTH levels are normal to undetectable, which implies the presence of a protein with PTH-like activity. Other biochemical abnormalities include decreased serum phosphorus and elevated serum chloride [21].

GRFoma

Growth hormone-releasing factor (GRF) secreting tumors cause acromegaly due to hypersecretion of growth hormone. They may secrete GRF alone or with other hormones. Growth hormone-releasing hormone is normally secreted by the hypothalamus and stimulates release of growth hormone from the pituitary. Patients with GRFomas have ages that range from 15 to 63 years with a mean age of 38.4 years. A female preponderance has been noted but is absent in classic acromegaly [22]. The acromegaly appears to resolve after extirpation of the tumor.

Neurotensinoma

Neurotensin is a 13-amino acid tridecapeptide found in the brain and gastrointestinal system. Its actions include stimulation of secretion by the small intestine and increase insulin release. It has also been implicated in the increase of venous vascular permeability and blood glucose as well as the decrease of blood pressure. Tachycardia and cyanosis are also effects of neurotensin. No physiologic role has been identified for this molecule as yet.

Neurotensin has been noted to be released by many pancreatic and intestinal tumors including glucagonomas, gastrinomas, and VIPomas [23]. They may also occur alone without the presence of other functioning endocrine tumors and appear to cause a syndrome of diabetes, hypotension, cyanosis, vasodilation, and edema. Hypochlorhydria, slowed gastric emptying, and secretory diarrhea might also be present. Biochemical investigation reveals hypokalemia, hypercalcemia, and high plasma neurotension-like immunoreactivity (NTLI) [19].

Association with Multiple Endocrine Neoplasia–1 Syndrome

MEN-1 syndrome is an autosomal dominant inherited syndrome that encompasses hyperparathyroidism due to multiple parathyroid adenomas, pancreatic neuroendocrine tumors, and pituitary adenomas [24]. The occurrence of rare functioning pancreatic tumors as a component of MEN-1 is uncommon. They comprise 3% of all pancreatic neuroendocrine tumors [25]. Of the functioning pancreatic neuroendocrine tumors, glucagonomas and VIPomas are estimated to be present in 3 and 1%, respectively. There have been a few reported cases of GRFomas occurring in MEN-1 as well [22]. It is important to note that any functioning pancreatic islet cell tumor is the most common cause of death in a patient with the MEN-1 syndrome. Thus, these patients need a rigorous screening program with early therapeutic intervention when a tumor is identified [26].

Management

Imaging

Computed Tomography or Magnetic Resonance Imaging

Computed tomography (CT) or magnetic resonance imaging (MRI) is generally employed as the initial diagnostic imaging evaluation in clinical practice. On unenhanced CT, the majority of tumors appear isodense and, thus, will not be seen unless the outline of the pancreas is deformed [27]. Dual-phase helical CT focused on the liver and pancreas improves detection rates due to different patterns of enhancement during early arterial, late arterial, and portal venous phases for visualization of primary tumor and distant metastasis [28].

MRI is often employed to detect tumors, confirm CT findings, and localize suspicious lesions that have not been demonstrated by CT. According to recent studies, MRI has a sensitivity of 94% for pancreatic lesions, which implies that CT and MRI have similar effectiveness in localization of tumors [29, 30].

Nuclear Medicine

Somatostatin receptor scintigraphy has become important in the staging of pancreatic neuroendocrine tumors to locate small foci of primary tumors and metastases since 55–95% of these tumors express somatostatin receptors [31]. This imaging modality utilizes the high-affinity binding of derivatives of somatostatin analogues like ^{111}In-DTPA-D-Phe^{1}-octreotide (DTPA-octreotide) to receptors over-expressed by these tumors. Newer peptides using indium (^{111}In), yttrium (^{90}Y), and gallium (^{68}Ga) for radiometal labeling have shown improvements in imaging times, radiation burden, and resolution of images when used for imaging, therapeutic, and positron emission tomography (PET) applications [32]. PET with the development of the CT/PET cameras have recently been shown to have higher detection rates when compared with conventional somatostatin receptor scintigraphy and diagnostic CT with a high degree of accuracy (96%) [33].

Other Imaging Modalities

Endoscopic ultrasound (EUS) and angiography with venous sampling have been used to localize small tumors that are not visible using other imaging modalities. EUS has a sensitivity of 82% and a specificity of 95% when localizing tumors less than 3 cm in diameter that are unable to be visualized on CT. EUS is the preferred modality for the screening of patients with asymptomatic, genetically proven MEN-1 syndrome [34]. With the advancements made in CT, MRI, and ultrasound technology, angiography, and venous sampling are used less frequently now.

Clinicopathologic Classification

In 1999, Solcia et al. proposed a classification system for pancreatic neuroendocrine tumors. It is based on the size of the tumor, its local proliferation rate determined by Ki67 index, and the presence of angioinvasion, gross local invasion, and metastases (Table 39.2) [35].

Table 39.2. Clinicopathologic classification of pancreatic endocrine tumors

Risk factor	Benign	Uncertain	Malignant
Size (mm)	<20	>20	>20
Ki67% index	<2	>2	>2
Local infiltration	No	Yes	Yes
Atypia	No	Yes	Yes
Angioinvasion	No	Yes	Yes
Gross invasion	No	No	Yes
Regional/distant metastases	No	No	Yes

Treatment

Treatment of pancreatic neuroendocrine tumors should be multimodal including surgery, radiation, and medical therapies. Since these tumors frequently cause indolent diseases, their condition may be managed symptomatically early on, and in some cases, no further treatment may be indicated, sparing patients from the impact on the quality of life as a result of surgery or medication side effects [36]. The treatment algorithm is summarized in Fig. 39.2.

Surgical Intervention

Surgical resection remains the mainstay of treatment, as indicated by the 95% 5-year survival rate for small, localized tumors. For more extensive disease, treatment depends on location. For example, enucleation may be appropriate for small tumors, while tumors originating in the tail of the pancreas can be resected by distal pancreatectomy.

Presence of metastases has a significant impact on survival. In a review of cases at Mayo Clinic over a 20-year period, 3-year survival for those with and without hepatic metastases was 56 and 82%, respectively [37]. However, management of hepatic metastases, which are common at the time of diagnosis, continues to be controversial. Among 87 patients treated at Sloan-Kettering Memorial, the 5-year survival was none for medical therapy, 50% with hepatic artery embolization, and 76% with resection. It also showed that palliative resection resulted in hormone reduction in all patients with 90% patients experiencing reduced pain [38]. It is accepted that hepatic resection should be attempted in cases where greater than 90% of the tumor may be removed. Liver transplantation has also been proposed for hepatic metastasis removal, revealing an

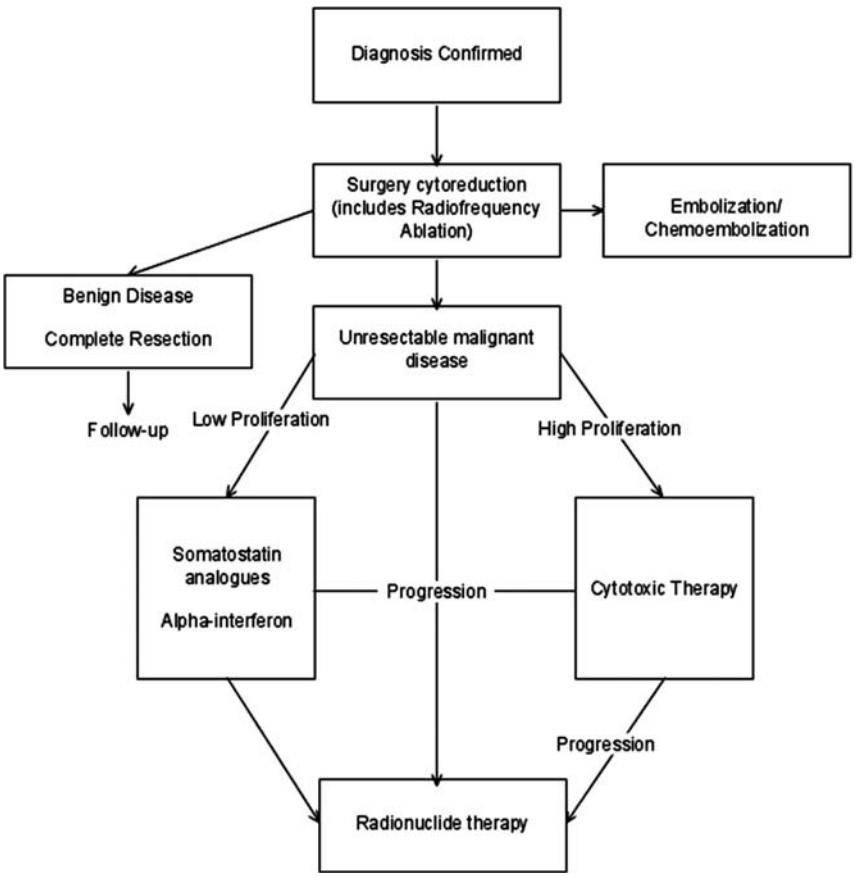

Fig. 39.2. Treatment algorithm for rare pancreatic functioning tumors. This algorithm can be used to help guide the therapeutic choices for patients with PET.

87% 2-year survival rate and an acceptable 23% 2-year estimated disease recurrence in one study [39].

Hepatic Artery Embolization and Chemoembolization

Hepatic artery embolization (HAE) is generally considered as a treatment option for patients with unresectable liver metastases, which include bilobar metastases, greater than 75% liver involvement, and extra-hepatic metastases [38]. Treatment is based on the principle that while the portal vein supplies most of the hepatic blood supply, tumor metastases preferentially derive their blood supply from the hepatic artery. Hepatic chemoembolization is the addition of the intra-arterial chemotherapy using agents such as 5-fluorouracil and streptozotocin and has been shown to have some benefit in this type of tumor [40]. Liver involvement greater than 50%, signs of liver failure, and portal vein thrombosis are contraindications of this treatment. To date, there have been no studies comparing the efficacy of HAE and hepatic artery chemoembolization (HACE), but current data show no substantial difference. A recent study showed that in 54 patients, HAE/HACE had a response rate of 35.2% and a cumulative 1-year, 2-year, and 5-year overall survival rates were 68.8, 48.7, and 13.7% [41]. Hormone levels have been shown to have been reduced in greater than 90% of patients; however these responses rarely lasted longer than 18 months [38].

Radiofrequency Ablation

Thermal ablation is a relatively new method of treatment that is minimally invasive and can reduce tumor bulk. It can be accomplished either laparoscopically or percutaneously. In a study at Middlesex Hospital, 186 tumors in 25 patients were treated with radiofrequency ablation (RFA) over 15 years. It demonstrated that tumor load was controlled in 74% of patients and relief of hormone-related symptoms was achieved in 69% of patients [42]. This suggests that RFA is a possible viable long-term treatment alternative for small tumors, since it is minimally invasive and easily repeated.

Radionuclide Therapy

As discussed before, radiolabeled somatostatin maybe used for both the diagnosis and the treatment of selected pancreatic functioning tumors. This is a newer treatment modality considered for inoperable tumors or those with medically uncontrollable symptomatology. The results in recent clinical trials using radiometals yttrium (^{90}Y) and lutetium (^{177}Lu) revealed complete and partial remission in up to 37 and 47% of patients, respectively [43, 44]. Side effect profile is similar to that of standard radiation therapy including nausea, vomiting, renal and liver toxicity, and lymphocytopenia.

Somatostatin Analogues

Systemic chemotherapy has been largely unsuccessful in palliation due to the decreased quality of life associated with the toxicity of treatment. Long acting somatostatin analogues like octreotide and lantreotide have been shown to be of some benefit in palliating the symptoms of glucagonomas, VIPomas, and other tumors except somatostatinomas. They may act by decreasing the quantity of hormone being released, reducing angiogenesis and activating the reticuloendothelial and lymphopoietic systems. In the case of glucagonomas, somatostatin analogues cause a lower severity of rash and is thought to be due to the effect of somatostatin on the skin. Symptomatic responses have been demonstrated to occur in 60–90% of patients treated with somatostatin analogues, but resistance to the treatment usually occurs within a year [45]. Mild side effects have been shown to occur, which include steatorrhea, cholelithiasis, and gastrointestinal disturbances. Tumor size reduction effects are minimal with less than 20% of patients showing tumor shrinkage [46].

Alpha-Interferon

Alpha-interferon (α-INF) acts by stimulating the immune system and has been applied to the treatment of many cancers. Its specific role appears to be enhancing natural killer cell function, increasing class I antigen and T-cell activity on tumors, and controlling hormonal symptoms. Side effects of trials have shown an objective response rate of 51% for a median duration of 20 months [47]. Recently, there has been an interest in combining somatostatin analogues and α-INF to increase their efficacy, since studies have shown an additive effect. A study of 16 patients with disease progression while being treated with somatostatin analogues and α-INF as single agent showed that more than 80% of patients benefited from the combined treatment with complete or partial response or stabilization for at least 10 months [48].

Circulating Tumor Markers

The tumor markers specific to each type of cancer are summarized in Table 39.3. Nonspecific tumor markers include chromogranin A,

Table 39.3. Tumors and their specific tumor markers

Tumor	Tumor marker
Glucagonoma	Plasma glucagons
	Plasma pancreatic polypeptide (PP)
VIPoma	Plasma vasointestinal polypeptide (VIP)
	Plasma peptide-histidine-methionine (PHM)
Somatostatinoma	Plasma somatostatin
ACTHoma	Plasma adrenocorticotrophin (ACTH)
CRHoma	Plasma/serum cortisol
PTHrPoma	Serum calcium
	Plasma parathyroid hormone-related peptide (PTHrP)
GRFoma	Plasma growth hormone (GH)
	Plasma/serum insulin-like growth factor-1 (IGF-1)
Neurotensinoma	Plasma neurotensin-like immunoreactivity (NTLI)

neuron-specific enolase, and alpha-subunits of the glycoprotein hormones. Particularly, the specificity of chromogranin A, which is a molecule secreted along with peptide hormones, for neuroendocrine tumors is high at around 80–100% [49]. The tumor markers are important for diagnosis, monitoring the effects of treatment and surveillance for recurrence.

Summary

The rare pancreatic functioning tumors are interesting cancers with unique clinical presentations caused by the hormones they secrete. Their diagnosis and management is confounded by their uncommonness, indolent growth, and presence of metastasis at the time of diagnosis. Surgery is the best option for cure, while other treatments like hepatic artery embolization, selective radiotherapy, and chemotherapy are good options for prolonging survival or palliating debilitating symptoms. There is still great potential for improvement in better characterization and diagnosis of the tumors as well as more directed and effective surgical and medical management.

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Laparoscopic Radiofrequency Ablation of Metastatic Neuroendocrine Tumors in the Liver

Jamie Mitchell, Eren Berber, and Allan Siperstein

Introduction

Neuroendocrine cells are distributed throughout the body and are unique regarding their histology, cytochemistry, and symptomatology. Tumors of these cells fall into two categories: those with the biology and natural history of a high-grade malignancy, such as small cell lung cancer, and those with a somewhat variable but more often indolent biological behavior and typically well-differentiated histology. The majority of these involve the gastrointestinal tract and include carcinoid tumors, pancreatic islet cell tumors, such as insulinomas, gastrinomas, and glucagonomas, paragangliomas, pheochromocytomas, and medullary thyroid carcinomas.

Despite their frequently indolent biology, up to 75% of patients with these tumors develop metastases to the liver, depending on the tumor type (carcinoid 5%, insulinoma 5–10%, glucagonoma 70–75%, and gastrinoma 23–90%). While surgical resection is the treatment of choice for liver metastases, most patients (>90%) cannot undergo curative resection due to the presence of extensive bilobar disease. However, many of these patients experience significant symptoms due to hormone hypersecretion, with octreotide therapy providing symptomatic relief in only a minority of patients. This, coupled with the indolent course of many of these tumors and the importance of palliation, has encouraged the application of regional treatment methods to the liver in these patients. One such treatment is radiofrequency thermal ablation, which has been shown to provide symptomatic relief in up to 90% of patients, with a median survival from the time of therapy of 3.9 years. The following chapter will describe the technical aspects of laparoscopic radiofrequency ablation of metastatic neuroendocrine tumors in the liver.

Surgical Anatomy

The ligaments of the liver include the falciform ligament, the right and left posterior coronary ligaments, and the right and left triangular ligaments. The hepatoduodenal ligament contains the extrahepatic bile duct system, the hepatic artery, and the portal vein. The portal vein is formed behind the pancreatic head by the confluence of the splenic vein, the superior mesenteric vein, and in a minority of the cases, the inferior mesenteric vein. The portal vein divides into a left and right branch in the liver. The three major hepatic veins – the right, the left, and the middle – are formed by the hepatic venous system that begins from the central vein. The middle hepatic vein lies in the main

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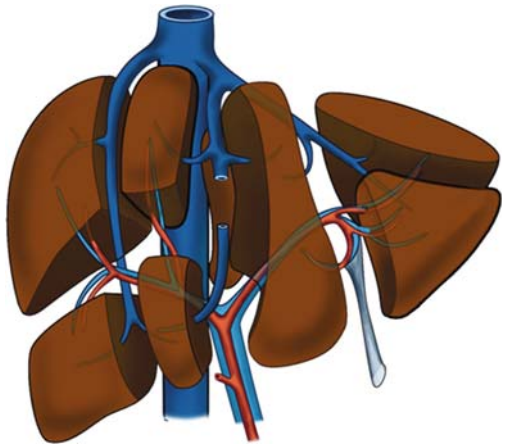

Fig. 40.1. Segmental anatomy of the liver.

lobar fissure, the left hepatic vein in the left segmental fissure, and the right hepatic vein in the right segmental fissure.

The liver is divided into two lobes by the main portal fissure, which extends from the gallbladder fossa to the left side of the inferior vena cava. The right portal fissure divides the right lobe into an anteromedial and posteromedial sector. The falciform ligament divides the left lobe into a medial and lateral segment. The liver is further divided into eight Couinaud segments. In this system, segment I, the caudate lobe, is autonomous receiving branches from both the right and the left portal vein and hepatic artery branches. The caudate venous drainage is independent and may drain directly into the inferior vena cava (Fig. 40.1).

Preoperative Considerations

Imaging

Patients should have a tri-phasic CT scan of the chest, abdomen, and pelvis within 1 week of planned laparoscopic radiofrequency ablation (RFA). This is important to assess for any significant progression of intra- or extrahepatic disease which might indicate an aggressive biology of disease where RFA would not offer significant improvement in survival.

Tumor Volume

The volume of metastatic disease in relation to total liver volume should be assessed. Generally, no more than 20% of the total liver volume should be ablated to prevent postoperative hepatic failure. When dealing with metastatic neuroendocrine tumors, the number of lesions is not as important as for colorectal metastases, where the presence of more than eight lesions represents an aggressive biology of disease such that radiofrequency ablation is less likely to be of benefit.

Location of Lesions

Note should be made of the proximity of lesions to important structures, such as major bile ducts or the gallbladder, which could affect surgical strategy.

Patient Preparation

Operating Room Setup

Two laparoscopic monitors are positioned at the head of the operating room (OR) table. The laparoscopic boom is placed to the left of the patient, along with the ultrasound machine and radiofrequency ablation generator (Fig. 40.2).

Positioning

Patients without allergies are given 1 g of a first-generation cephalosporin (cefazolin) as antimicrobial prophylaxis. Patients are positioned supine on the OR table, and once general endotracheal anesthesia is established, the patient's abdomen is shaved using clippers. If there are many lesions to treat (greater than 4) where long operative times are anticipated, it is prudent to place a Foley catheter. Otherwise, this is generally not necessary. Patients with hormonally active neuroendocrine metastases, such as insulinoma or carcinoid tumor, should be managed accordingly.

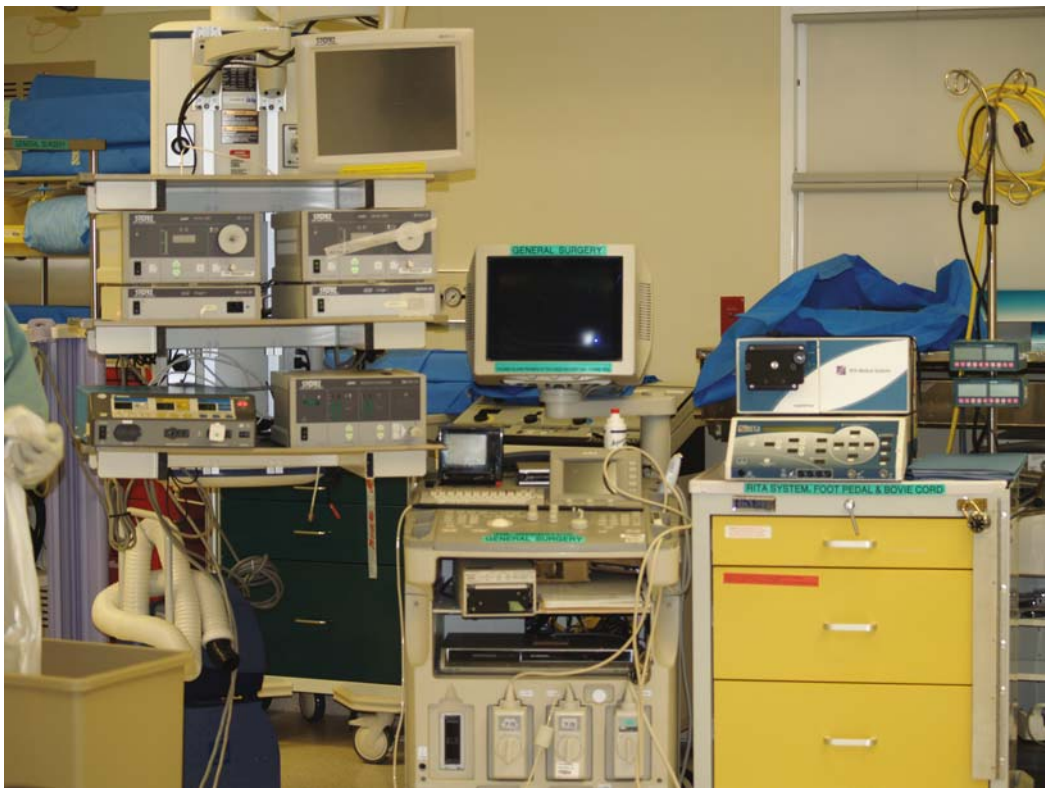

Fig. 40.2. Operating room setup.

Thermo pad Placement

Thermo pads are placed on the anterior and posterior aspect of the thigh of both lower extremities. These contain thermo-couples that allow the RFA generator to continually monitor the patient temperature at these sites while heat is being generated during the procedure. This allows the ablation cycle to be stopped if patient temperatures reach unsafe levels. If possible, the arms are tucked, and the abdomen is then prepped and draped in the usual fashion.

Operative Technique

Trocar Placement

Two 11-mm trocars are placed approximately 2–3 fingerbreadths below the right costal margin. One port is for the laparoscope, the other for the ultrasound probe. We gain access to the peritoneal cavity under direct vision using an optical access trocar and a 10-mm/0° laparoscope. This is a safer option considering that majority of these patients have had previous abdominal surgery (see Fig. 40.3).

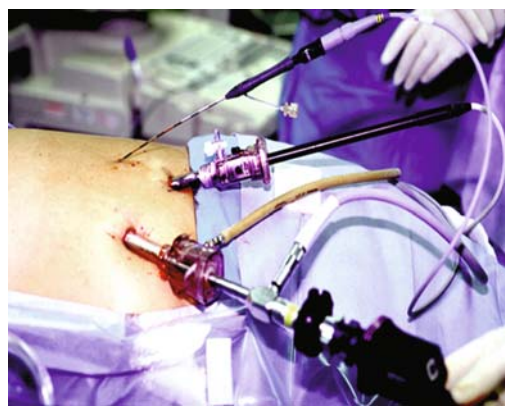

Fig. 40.3. Intraoperative view with typical trocar positioning.

Diagnostic Laparoscopy

After gaining safe access to the peritoneal cavity, pneumoperitoneum is established. The laparoscope is exchanged for a 10-mm/45° version, and diagnostic laparoscopy is performed to assess for extrahepatic disease. While the presence of mild extrahepatic disease does not preclude further therapy with radiofrequency ablation, widespread disease or carcinomatosis does.

Ultrasound Examination

Next thorough ultrasound examination of the liver is performed. Known lesions seen on preoperative imaging studies are identified, and the presence of additional lesions is determined. In approximately 20% of cases, intraoperative ultrasound examination will detect additional lesions not seen on tri-phasic CT scan. We use a rigid 10-mm linear side-viewing transducer, and it is important to systematically scan the entire liver, either in a territorial or in a segmental fashion.

Biopsy

We next perform a core needle biopsy of one of the lesions to confirm metastatic disease. This is performed by targeting the lesion with the ultrasound probe. The monitor is configured for picture-in-picture viewing with a quarter-sized laparoscopic image with a full-sized ultrasound image to coordinate movements of the probe with the laparoscopic image.

Once directly over the lesion, the probe is rocked in both directions to gain a sense of its center. Next an 18-G spring-loaded biopsy gun is percutaneously inserted into the peritoneal cavity. This is done as close to the costal margin as possible and along the same trajectory as the ultrasound probe, allowing you to visualize the path of the needle much more easily (Fig. 40.4). Try to choose a trajectory which avoids major vessels or bile ducts.

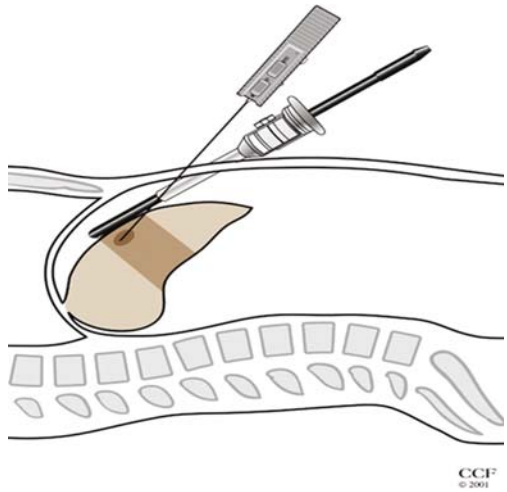

Fig. 40.4. Core needle biopsy of liver lesion.

Once the biopsy needle is satisfactorily positioned at the center edge of the lesion, it is fired. Confirm adequacy of sample by visualizing the trajectory of the deployed needle through the lesion with the ultrasound as well as by visual inspection of the tissue. Send for frozen section analysis (Fig. 40.5).

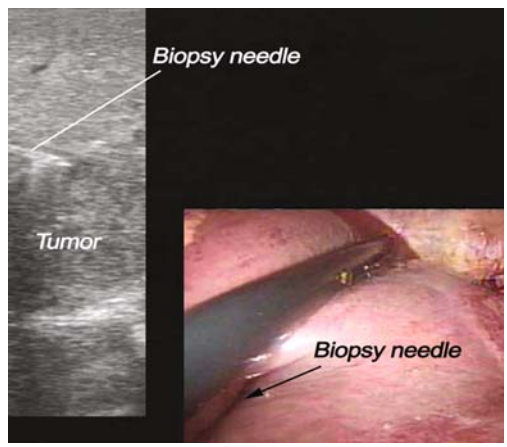

Fig. 40.5. Intraoperative picture-in-picture view of core needle biopsy.

Radiofrequency Ablation

Next the radiofrequency ablation catheter is prepared. While the principles are the same, several different ablation catheters are available, such as straight tip electrodes or needles with deployable prongs with or without thermocouples (Fig. 40.6). We routinely use the 5 cm, 9-pronged catheter with 5 thermocouples (Fig. 40.7).

The ablation catheter is inserted along the same trajectory established during biopsy, employing the same principles. The catheter is positioned at the center edge of the lesion and deployed to 2 cm (Fig. 40.8). The generator then delivers radiofrequency energy to the prongs to create heat. The front panel of the generator displays important ablation parameters, such as the temperature at the 5 thermocouples, the maximum power being delivered, time at target temperature, total ablation time, and impedance (Fig. 40.9).

Once the cycle is complete, one must assess for adequacy of the ablation. This is done by observing nitrogen outgassing from the ablated tissue, seen as a hyper-echoic blush. This should encompass the lesion completely (Fig. 40.10). Additionally, one should observe the temperature of the tissue following the ablation cycle. Temperatures remaining above 50°C 1 min after termination of the ablation cycle are indicative of adequately ablated tissue. The prongs are un-deployed, and the ablation catheter is withdrawn from the lesion. The tract may be coagulated with 20–30 W of power from the generator to stop any troublesome bleeding.

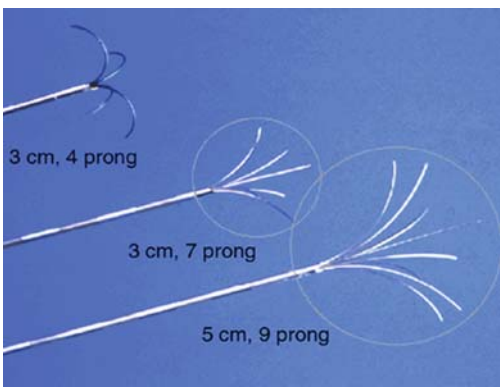

Fig. 40.6. Types of radiofrequency ablation catheters. Volume: 3 cm, 14 cc; 5 cm, 65 cc.

Postoperative Care

Postoperatively, patients are placed on a regular diet and typically discharged on POD 1. Routine labs are drawn on the morning of POD 1, including CBC, complete metabolic panel, PT/PTT, liver function panel, and tumor markers as appropriate. Patients are

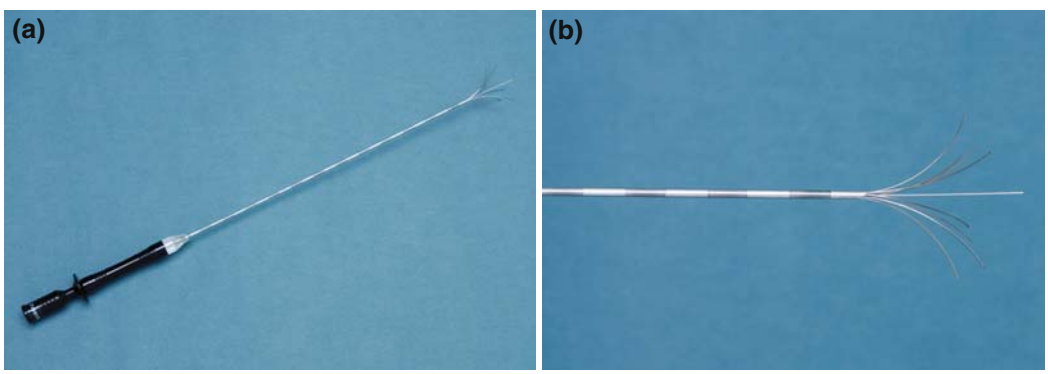

Fig. 40.7 (**A**, **B**) 5 cm, 9-pronged radiofrequency ablation catheter.

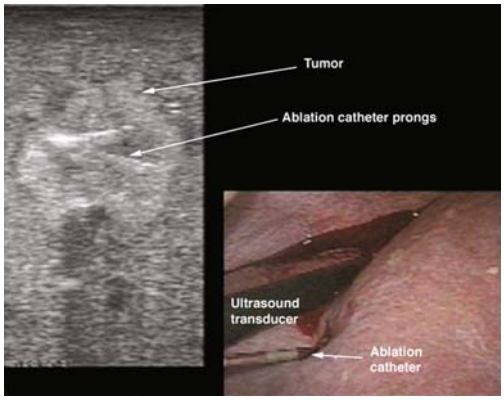

Fig. 40.8. Ultrasound image of ablation catheter in lesion with prongs deployed.

seen in the office 1 week after surgery for a triphasic CT scan and another set of labs. These are all repeated at 3-month intervals for ongoing surveillance for recurrent disease.

The ablation zone should appear as a low attenuation area in the liver, and these should slowly decrease in size over time. Ablation zones which increase in size or display new areas of enhancement are suspicious for locally recurrent disease (Fig. 40.11).

Pearls and Pitfalls

Lesions in the Dome of the Liver

Lesions high in the dome of the liver can present more of a technical challenge. These lesions are often adjacent to the diaphragm, placing this structure at risk for injury during ablation. These lesions can also be difficult to image with the ultrasound transducer, as it is often difficult to get adequate contact with the surface of the liver in this region. By infusing saline into the

Fig. 40.9. Panel display of radiofrequency ablation generator.

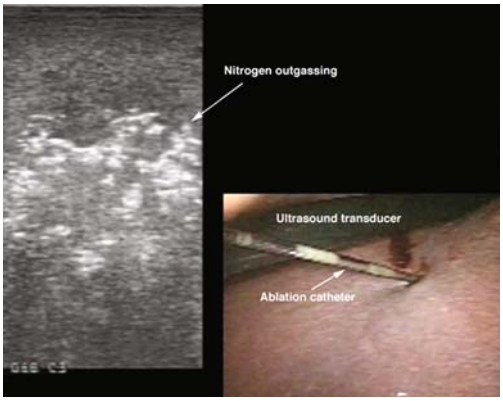

Fig. 40.10. Ultrasound view of nitrogen outgassing during ablation cycle.

suprahepatic space, an acoustic window is created which allows the lesion to be visualized. This also creates a small buffer between the lesion and the diaphragm, decreasing the risk of injury (Figs. 40.12 and 40.13).

Lesions Near the Gallbladder

Any lesions adjacent to the gallbladder fossa will put the gallbladder at risk for injury during ablation. When this possibility exists, it is safest to perform a cholecystectomy prior to ablation.

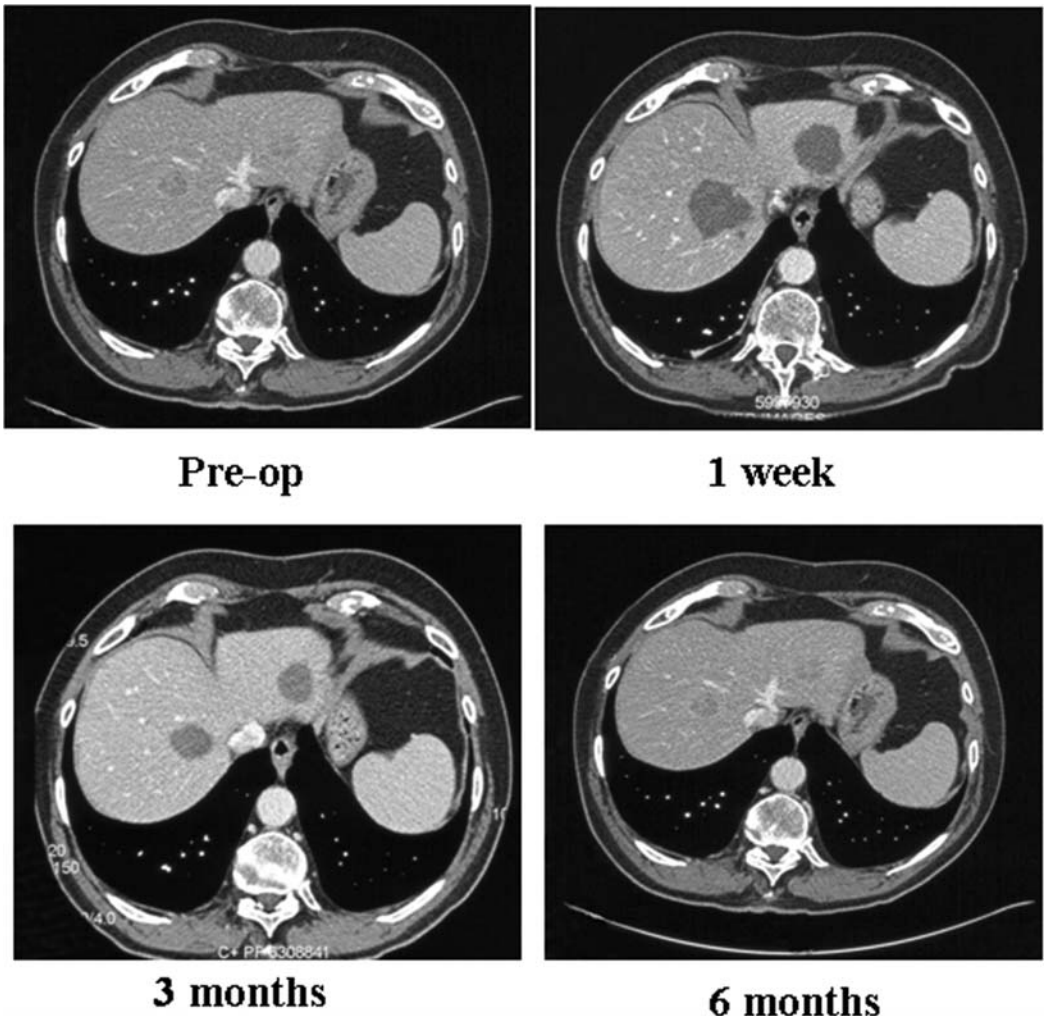

Fig. 40.11. Postoperative surveillance with tri-phasic CT scan.

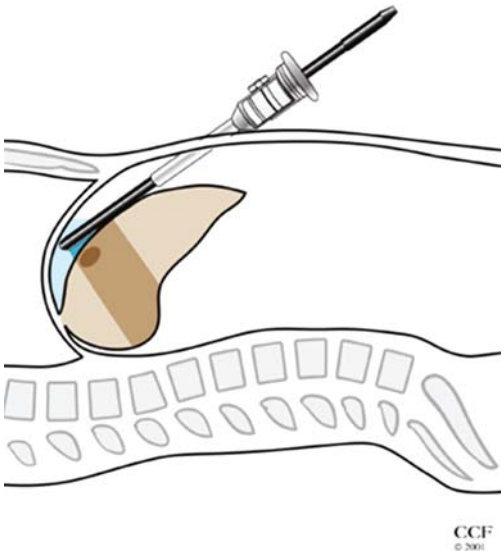

Fig. 40.12. Use of saline to facilitate imaging of lesions in dome of liver.

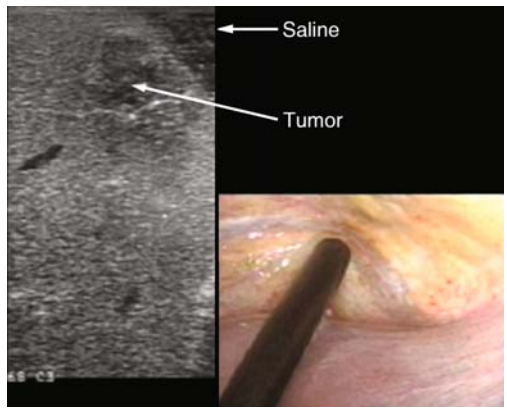

Fig. 40.13. Interoperative use of saline for lesions high in the dome of the liver.

Lesions Near Main Portal Vein Branches

Lesions near any of the main portal vein branches must be approached with caution. While the portal vein is not at risk of injury during ablation, the bile duct branches that accompany these portal vein branches are. One can come within a few millimeters of the ductal structures with the ablation, but this must be very precise. The larger bile duct branches can usually be seen on ultrasound, with the use of color flow Doppler exam being particularly useful here.

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Pancreatic Incidentaloma

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Mauricio Sierra Salazar,
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Introduction

The widespread use of highly sensitive imaging techniques has led to the serendipitous identification of subclinical tumors in some organs [1]. Pancreatic incidentaloma (PI) has been defined as a mass that is incidentally discovered during an image study for symptoms other than the ones of the mass itself or the organ affected. The term "pancreatic incidentaloma" was first described by Ho and Kostiuk [2, 3]. The incidence of PI varies among different studies. In a series of 333 asymptomatic potential kidney donors, two cases of PI (0.6%) were found [4]. In a recent report analyzing the Japanese experience of PET for cancer screening in 39,785 asymptomatic subjects, six cases of unsuspected pancreatic cancer (0.01%) were discovered [5]. Some studies have suggested that the incidence is rising [6].

When encountering a PI, the aim is to determine the benign or malignant nature of the lesion. There is a general idea that early treatment of incidental malignant lesions may render a higher cure rate and prolonged survival. However, series studying subclinical tumors in different organs have shown that the rate of malignancy and the impact of early treatment vary. The outcome is thus related not only to the stage of the disease at the time of diagnosis but also to the biologic aggressiveness of the tumor.

Some authors have suggested that the identification and early treatment of an incidental lesion in certain organs, such as the kidney, reduces morbidity and mortality. In a study of 633 patients with renal carcinoma, earlier stages were significantly more frequent, and the 5-year cancer-specific survival rate was higher in the 15% of tumors discovered incidentally, when compared with patients with overt disease [7].

Studies analyzing the benefit of identifying hepatic incidentalomas have reported contradicting results. Little and colleagues in a series of 64 hepatic incidentalomas found that only 11 (17%) of patients were benefited from the early identification of a tumor. In contrast, 83% of the patients did not experience any benefit in terms of quality of life or prolonged survival [8]. Lui et al., in a study where 58% of hepatic incidentalomas were malignant, found that patients with hepatocellular carcinoma had a significantly better survival than those patients with clinically suspected malignancy who underwent treatment during the same period of time [9].

Obsessive search for small incidental tumors has, on the other hand, the risk that a significant number of patients may undergo extensive diagnostic evaluation and treatment without any positive impact on their health status, with the added risk of well-known surgical complications [10].

Etiology of PI involves a variety of benign and malignant diseases, which are depicted in Table 41.1. Demographic characteristics of PI located in the pancreatic head (age, gender, and comorbidities) have been shown to be similar to those of patients with symptomatic

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Table 41.1. Etiology of pancreatic incidentaloma

Exocrine

Benign
- Serous cystadenoma
- Mucinous cystadenoma
- Intraductal papillary mucinous adenoma
- Mature cystic teratoma

Borderline
- Mucinous cystic tumor with moderate dysplasia
- Intraductal papillary mucinous tumor with moderate dysplasia
- Solid pseudopapillary tumor

Malignant
- Ductal adenocarcinoma
- Osteoclast-like Giant Cell tumor
- Serous cystadenocarcinoma
- Mucinous cystadenocarcinoma
- Intraductal papillary mucinous carcinoma
- Acinar cell carcinoma
- Pancreatoblastoma
- Solid-pseudopapillary carcinoma
- Ampullary adenocarcinoma

Endocrine
- ACTH secreting tumor
- Carcinoid tumor
- Gastrinoma
- Glucagonoma
- GRF-secreting tumor
- Insulinoma
- PP secreting tumor
- Somatostatinoma
- VIPoma

Cystic lesions
- Benign pancreatic cysts
- Dysontogenic cysts
- Hydatid cyst
- Lymphoepithelial cysts (LECs)
- Pancreatic dermoid cysts
- Parasitic cysts (echinococcus granulosis and multilocularis cysts)
- Retention pancreatic cysts

Congenital
- Choledochocele cyst
- Congenital cyst
- Intrapancreatic accessory spleen

Infectious masses
- Ascaris lumbricoides
- Candida albicans
- CMV
- Coxsackievirus
- Cryptosporidiosis
- Mumps
- Mycobacterium avium complex
- Mycobacterium tuberculosis

Mesenchymal tumors
- Kaposi's Sarcoma
- Lipoma
- Lymphangioma
- Pancreatic Castleman's disease
- Pancreatic hamartoma
- Pancreatic sarcoma
- Plexiform neurofibroma
- Schwannoma
- Teratoma

Metastatic lesions
- Breast
- Colon
- Lung
- Lymphoma
- Melanoma
- Renal cell carcinoma

Nonislet cell tumors
- Adenosquamous carcinoma
- Anaplastic tumors
- Clear cell "sugar" tumor
- Colloid carcinoma
- Granulocytic sarcoma
- Leukemia
- Lymphoma
- Primitive neuroectodermal tumor

Pancreatic inflammatory mass
- Eosinophilic pancreatitis
- Focal pancreatitis
- Inflammatory myofibroblastic tumor
- Lymphoid hyperplasia
- Phlegmon
- Pseudocyst
- Traumatic pancreatitis
- Wagener's disease
- Xanthogranulomatous pancreatitis

pancreatic tumors [6]. The rate of malignancy in PI has been reported to be as high as 32%, which is higher than the percentage of malignancy reported in other organs such as the liver, the kidney, and the adrenal glands [6–11]. The malignancy rate of PI (32%) is lower than the percentage found in patients with clinical suspicion of a PC (75.9%) [6]. When TNM staging was compared, the PI group also had a significantly higher proportion of patients in lower stages (stage I, 34.4 vs 10.4%) and significantly fewer positive lymph nodes. Adjusted survival rate after resection in this study was also significantly higher in patients with PI than in symptomatic patients [6]. These findings favor a more aggressive approach toward PI.

The term "imaging incidentalomas" has been proposed for the tumors identified by conventional imaging techniques. Asymptomatic pancreatic masses can also be identified by endoscopy or endoscopic ultrasound (US), giving them the name "endoscopic incidentalomas" [6]. Series where PI have been detected by endoscopy show a higher percentage of ampullary and neuroendocrine tumors.

PI can be grossly divided into solid or cystic. We discuss both groups separately.

Solid Tumors

The incidence of benign disease in solid pancreatic tumors suspicious of cancer ranges from 6 to 21%. Chronic pancreatitis accounts for almost 70% of the benign lesions [12], alcoholic pancreatitis being the most common cause (60%). In the past, the diagnosis of "idiopathic pancreatitis" was established in one third of the cases. It is now known that up to 11% of those patients have autoimmune pancreatitis [13–15]. Specific characteristics on image studies can help to differentiate malignant from benign lesions.

The likelihood of identifying a PI on an image study depends basically on three factors. One is tumor features such as size, density, echogenicity, calcifications, and duct dilatation. The second is the quality of the study, and the last one is the experience of the person interpreting the study [16]. All three factors are of atmost importance, since it has been described that changes compatible with malignancy occur as early as 18 months before diagnosis [17].

In the following sections we describe relevant image features of pancreatic tumors that may be of help to the differential diagnosis.

Pancreatic Cancer

The most frequent solid lesion in the pancreas is pancreatic carcinoma (PC). At the time of diagnosis in symptomatic patients, advanced disease is the most frequent scenario (extensive local disease in about 40% and metastases in 40–55%), leaving less than 20% of patients as candidates for potentially curative resection [18, 19]. The earliest imaging finding of a PC before a mass becomes apparent is pancreatic duct dilatation or pancreatic duct cutoff [17].

On the arterial phase of a dynamic helical CT scan, PC presents as a hypovascular, hypoenhanced lesion when compared with the surrounding pancreatic parenchyma [20, 21]. Necrosis may be present in larger tumors, and it is represented by nonstaining areas in the center of the mass. When these findings are present, the hypodense mass is highly likely to be ductal carcinoma [20]. When the disease is more advanced it can show local invasion or vascular encasement [21]. Multidetector row spiral CT allows for a better and faster image acquisition, leading to more refined images.

The sensitivity and specificity of FDG PET for the diagnosis of PC in patients with normal blood glucose levels range from 85 to 100% and from 67 to 99%, respectively. False-positive studies are associated with the presence of inflammation or history of radiation, and false-negative studies can occur in patients with hyperglycemia and in some small tumors. In contrast with CT alone where size is an important factor, FDG PET sensitivity is independent of tumor size. Recent reports have shown that the amount of FDG uptake may be of prognostic value. Combination of PET and CT may offer a better accuracy [22–23].

Most PC on MRI are hypointense on unenhanced T1-weighted sequences when compared with the surrounding pancreas, and they are hypointense or isointense on T2-weighted images. Unfortunately, up to 44% of PC can be mildly hyperintense on T2-weighted images, which causes some confusion [24].

Sensitivity and specificity of simple MRI and CT scan in the evaluation of solid pancreatic masses are similar [19, 22]. Magnetic resonance

cholangiopancreatography can be added to better define pancreatic duct characteristics, and angiography to assess vascular involvement. Time–signal intensity curve on MRI may help to distinguish PC from chronic pancreatitis when there is a focal mass in the pancreas and to identify a PC in patients with long-standing chronic pancreatitis [25].

On endoscopic US, PC is often observed as a hypoechoic, nonhomogeneous irregularly shaped mass when compared with the surrounding parenchyma. Tumors less than 2 cm may have a more homogeneous echogenicity and smooth borders [26]. Factors associated with failure to detect PC on endoscopic US include the presence of chronic pancreatitis, diffuse infiltration of the tumor, and recent history of acute pancreatitis [27]. In a recent study, the sensitivity of endoscopic US and multidetector row spiral CT for detecting a pancreatic tumor was 98 and 86%, respectively. Tumors smaller than 25 mm were detected more frequently by endoscopic US [28]. In a different study where endoscopic US was compared with MRI and PET, sensitivity was 98, 87.5, and 87.5%, respectively [29].

Endoscopic US has the possibility of performing US-guided fine-needle aspiration with a sensitivity from 64 to 98% and a specificity from 71 to 100% for the cytological diagnosis of PC [12, 19]. The overall rate of complications of the procedure ranges from 2 to 5% [30, 31]. Chronic pancreatitis can be a confounding factor. In a recent study, sensitivity of fine-needle aspiration for detecting PC in patients with and without chronic pancreatitis is 73.9 and 91.3%, respectively [32].

Serum tumor markers can be helpful in differentiating benign from malignant pancreatic masses. The addition of other tumor markers such as Ca-125 does not increase the diagnostic accuracy of Ca 19-9 is the gold standard marker for PC with a sensitivity and specificity as high as 87 and 98%. False-positive diagnosis can occur in the presence of hyperbilirubinemia, and false-negative diagnosis can be established in patients with rare blood groups (Le(a−b−) blood group) and fucosyltransferase deficiency. The combination of Ca 19-9 with other tumor markers such as Ca 125 does not increase the diagnostic accuracy [33]. Promising studies of plasma proteomic profile, DNA array, and micro RNA expression may be used for the early detection of PC and for the differential diagnosis between PC and chronic pancreatitis [34–37].

Islet Cell Tumors

In general, ICT are rare. They account for 2–4% of all pancreatic neoplasms with an incidence of 1.5 in 100,000 inhabitants. Nearly 60% secrete one or more biologically active peptides, resulting in clinical syndromes. The most frequent functioning tumors are insulinoma, gastrinoma, glucagonoma, VIPoma, and somatostatinoma. Because each has a different clinical presentation and some specific image characteristics, it is not frequent that diagnosis of an unsuspected functioning ICT by imaging studies only is made.

Between 30 and 40% of ICT are nonfunctioning, and this is more likely to be discovered incidentally when symptoms due to the presence of the mass are not yet obvious [38]. Multiple ICT are generally associated with other endocrinopathies as part of the multiple endocrine neoplasia or the Von Hippel-Lindau syndromes.

On CT scan, most ICT present as isodense or moderately hypodense masses with important IV enhancement. Calcification, necrosis, and cystic degeneration seem to be more common in large nonfunctioning tumors. It is important to acquire images in arterial, venous, and portal phases. The portal phase has proven to be the phase in which most small tumors can be identified [39].

MRI has a diagnostic sensitivity of 78–91% [16, 40], which is equivalent to dynamic CT [40]. MRI, on the other hand, is more sensitive than CT for liver and bone metastases [41]. ICT show low signal intensity on T1-weighted images and high signal intensity on T2-weighted images [24, 42, 43].

Endoscopic US can identify lesions as small as 5 mm in size. Tumors located in the tail of the pancreas are less likely to be identified by endoscopic US [40, 44, 45]. In a recent prospective study, sensitivity and specificity of endoscopic US was 93 and 95%, respectively [45].

Scintigraphy using ^{111}In-octreotide has shown to have a sensitivity of 67–91% for the detection of ICT, and it is used for diagnosis, staging, and follow-up [40, 46, 47]. ^{11}C-5-hydroxytryptophan PET has recently shown good results in detecting small gastrinomas and nonfunctioning ICT [48].

Pancreatic Metastases

Metastases to the pancreatic parenchyma are uncommon. The incidence of patients with advanced malignant tumors in autopsy studies varies from 3 to 12%. The more frequent tumors metastasizing to the pancreas are renal cell, bronchogenic, and breast carcinomas as well as melanoma; they can be found as part of the initial work-up for their primary tumor or during follow-up. Time interval between the primary lesion and the pancreatic metastatic disease can be up to 20 years, particularly in patients with renal cell carcinoma [49, 50].

On CT scan, pancreatic metastases can have three different patterns. The most common presentation is as a single mass (50–73%). Lesions have well-defined margins and tend to be ovoid. They are isodense or hypodense on the noncontrasted phase. Vascular invasion is rare. However, splenic vein obstruction and portal hypertension have been reported. Irregularities in the main pancreatic duct can also occur, making it difficult to differentiate metastases from chronic pancreatitis. Another form of presentation is as a diffuse enlargement of the pancreatic gland (15–44%). The presence of multiple pancreatic masses is the least common presentation (5–10%) [50]. IV enhancement of the metastases seems to correlate with the enhancement characteristics of the primary tumor [50]. On MRI, metastases are frequently hypointense on T1 and hyperintense on T2. On endoscopic US metastatic lesions are hypoechoic or isoechoic, round, and well-defined [51]. In a series of 23 patients with pancreatic metastases from renal cell carcinomas, 52% were diagnosed in asymptomatic patients at follow-up of, and 44% in patients with suspicion of recurrence [52]. Metastases to other organs can be as frequent as 95%. This finding supports the metastatic nature of the disease [50].

Chronic Pancreatitis

Morphologic changes due to chronic inflammation of the pancreas are atrophy of the parenchyma and calcifications. Focal enlargement and the development of a pancreatic mass may also occur. Chronic pancreatitis often represents a real dilemma since it may resemble a pancreatic tumor.

When fibrosis is present, it is uniformly distributed throughout the entire gland. If fibrosis is nonuniform, it may resemble a pancreatic mass on image studies. Although there has been intensive research in this field, it is still very difficult to differentiate PC from chronic pancreatitis [53].

Endoscopic US criteria for chronic pancreatitis include at least three of the following findings: heterogeneous echogenicity, lobularity, lobular gland margins, hyperechoic stranding, hyperechoic foci, duct irregularity, atrophy, the presence of a cyst, stone, calcifications, ductal dilation, or side branch dilation [54]. In a recent study FDG PET had a sensitivity and specificity of 100 and 97%, respectively, for the diagnosis of chronic pancreatitis and 96 and 100% for PC [55].

Autoimmune pancreatitis occurs in 4–11% of patients with chronic pancreatitis [14]. Up to 33% of patients with autoimmune pancreatitis may present a discrete mass mimicking a pancreatic tumor. High serum level of γ-globulin, IgG, IgG4, or the presence of positive autoantibodies including antinuclear, antilactoferrin, and anticarbonic anhydrase antibodies, and rheumatoid factor can help for the diagnosis. When a biopsy is performed, marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the periductal area are present [56]. A summary of image characteristics is shown in Table 41.2.

Cystic Tumors

Most cystic lesions of the pancreas are benign [57–59]. It is important, however, to characterize such lesions and to distinguish true cystic lesions from pancreatic pseudocysts. The different histologic types of pancreatic cystic neoplasms are shown in Table 41.3. Serous cystadenomas, mucinous cystic lesions, and intraductal papillary mucinous neoplasms account for more than 90% of primary cystic pancreatic tumors [58]. Whilst pure cystic asymptomatic lesions are benign and can be safely followed, mucin-producing lesions are potentially malignant and warrant surgical resection [57–59].

Most cystic pancreatic lesions are incidentally found on imaging studies performed for other pathologies, and as many as 35% of patients are totally asymptomatic at the time of discovery [57–59].

Table 41.2. Differential diagnosis of solid tumors

	CT	FDG-PET	MRI	Endoscopic US	Confounding factors
Pancreatic carcinoma	• Hypovascular • Hypoenhanced in arterial phase	• Focal FDG uptake	• T1 hypointense, T2 hypo- or isointense	• Hypoechoic, non homogeneous, irregular shape	• T2 Mild hyperintensity in 44% of Mets and ICT
Islet cell tumors	• Iso- or hypodense w/o contrast • Important contrast enhancement • In MEN multiple lesions	• Variable uptake depending on the tumor • Limited accuracy (better accuracy with 5-hydroxitryptophan)	• T1 hypointensity T2 hyperintensity	• Homogeneous, regular shape hypoechoic	• Multiple can also be Mets
Metastases	• Well defined margins • Ovoid, iso- or hypodense w/o contrast • Diffuse enlargement • Multiple lesions	• Focal uptake depending on the primary tumor	• T1 hypointense • T2 hyperintense	• Hypo- or isoechoic well-defined round lesions	• Multiple can be ICT associated with MEN
Chronic pancreatitis	• Atrophy, calcifications	• Diffusely increased uptake	• Atrophy, calcifications	• Heterogeneous echogenicity, hyperechoic stranding	• Focal pancreatitis can be mistaken with PC

Table 41.3. Image patterns for cystic pancreatic tumors with clinical association

Lesion	Morphology	Associated lesion	Management
Unilocular cysts	• No septa • Solid component • Central-cyst wall calcification	• Pseudocyst • IPMNs • Unilocular serous cystadenomas • Lymphoepithelial cysts	• Observation if <3 cm • EUS cyst content analysis of suspicious lesions
Microcystic	• Polycystic or microcystic pattern (>6 compartments) • Stellate pattern calcification	• Serous cystadenoma	• Observation
Macrocystic	• Multilocular (<6 compartments) • Larger compartments	• Mucinous cystadenomas • IPMNs	• Surgery
Solid component	• Uni or multilocular with solid component	• Mucinous cystadenomas • IPMNs	• Surgery

Symptomatic patients may refer abdominal pain as the chief complaint. Jaundice is infrequent and is usually associated with large lesions obstructing the common bile duct. Recurrent episodes of pancreatitis can be related to the abdominal pain episodes [57–60].

Following Bosniaks classification for renal cysts, a radiographic classification of pancreatic cysts based on imaging features was proposed [61]. Accordingly, the four different types of cystic lesions recognized today are (1) unilocular cysts, (2) microcystic lesions, (3) macrocystic lesions, and (4) mixed lesions or cysts with a solid component. This classification has both diagnostic and therapeutic implications, associating the radiographic features with the specific clinical entities, and eventually defining the therapeutic approach.

Unilocular Cysts

Pancreatic pseudocysts are the most commonly found unilocular cysts. Others include intraductal papillary mucinous neoplasms, serous cystadenomas, and lymphoepithelial cysts [62, 63]. The absence of clinical symptoms or laboratory or imaging signs related to pancreatitis may help to differentiate true cystic lesions from pseudocysts. A unilocular lesion in a patient with a clinical history of pancreatitis is almost always a pseudocyst. A thin-walled pancreatic duct is consistent with the diagnosis. MRI cholangiopancreatography or fine cut CT may find communication between the pseudocyst and the pancreatic duct. A lobulated unilocular cyst located in the head of the pancreas should raise the suspicion of a serous cystadenoma [63].

Microcystic Lesions

Serous cystadenoma usually demonstrate a polycystic or microcystic pattern consisting of a cyst collection that ranges from few millimeters to 2 cm in size [64]. They are usually lobulated. The septa and wall are enhanced on imaging studies. A stellate pattern of calcification is visible in 30% of the patients and is considered characteristic of a serous cystadenoma [64–69]. Pancreatic duct dilation is rare. In 20% of the cases, a honeycomb or sponge pattern is found on CT scan as a result of the microcystic nature of the tumor [64, 65]. In patients with indeterminate findings, MRI or endoscopic US can help to characterize the lesions. A similar honeycomb pattern can also be found on T2-weighted MRI images. Endoscopic US usually shows discrete small anechoic areas [65, 67, 68]. The benign nature of these lesions allows follow-up in asymptomatic patients [59, 69].

Macrocystic Lesions

Mucinous cystic neoplasms (cystadenomas) and intraductal papillary mucinous neoplasms usually present as macrocystic lesions. Mucinous cystadenomas mainly involve the body and tail of the pancreas. They do not communicate with the main pancreatic duct, but they can cause partial ductal obstruction [69]. MRI and/or endoscopic US are helpful in defining the architecture of the cyst, which helps to differentiate them from serous cystadenomas [64, 70, 71]. A peripheral eggshell calcification is highly suggestive of a potentially malignant mucinous cystic neoplasm [71]. Only 25% of patients are symptomatic at the time of diagnosis. Surgical treatment is advocated for all mucinous lesions [57, 59, 69. 72]. Patients with totally resected malignant tumors have a 50–75% long-term survival [57, 59, 69. 72].

Cysts with a Solid Component

Intraductal papillary mucinous neoplasms can be classified as main duct, branch duct, or mixed lesions. Side branch or mixed tumors are lesions that extend outside the main pancreatic duct. It may be difficult to differentiate them from a mucinous cystic neoplasm because they both share similar morphological features. MRI is considered the best modality to characterize these tumors. Endoscopic retrograde colangiopancreatography (ERCP) is seldom needed today for diagnosis. Computed tomography, with high-resolution multidetector row technology, can help to define the morphologic features of the cyst [61, 73]. These lesions are

Table 41.4. Cystic fluid aspirate analysis, biologic markers with malignant potential and probable clinical diagnosis

Marker	Cutoff levels	Probable diagnosis	Malignant potential	Experimental markers
Amylase	>5,000 U/l	Pseudocyst	Low	–
Ca 19-9	>50,000 U/ml	Mucinous cystadenoma	High	kRAS LOH analysis
CEA	>400 ng/ml	Mucinous cystadenoma	High	kRAS LOH analysis
CEA	<5 ng/ml	Serous cystadenoma	Low	VHL testing
Ca 72.4	>40 U/ml	Mucinous cystadenoma	High	kRAS LOH analysis
Mucin	>1,200/ml	Mucinous Cystadenoma	High	kRAS LOH analysis

VHL: Von Hippel-Lindau gene mutation, LOH: Loss of heterozygosity at chromosome 3p25; kRas: kRAS mutation.

considered premalignant and surgical treatment is thus advocated [58, 59, 74]. The incidence of malignancy is higher in main duct and mixed tumors than in side-branch neoplasms [75].

Cysts with a solid component can be unilocular or multilocular. Included in this category are true cystic tumors as well as solid pancreatic neoplasms with a cystic component or cystic degeneration. The latter include islet cell tumors (ICT), solid pseudopapillary, adenocarcinoma, and metastasis. Most tumors in this category are malignant and should be surgically treated [59, 76]. MR cholangiopancreatography is superior to single-section helical CT to characterize these tumors [75]. For small mural nodules, typically undetected by MR or CT scanning, high-resolution US is extremely sensitive.

Endoscopic US

When the image techniques cannot establish a definitive diagnosis, endoscopic US may add more detailed information about the lesion [77–79]. It is important to realize that endoscopic US can only differentiate solid from cystic lesions but cannot make the differential diagnosis between benign and malignant tumors. Cytological examination and fluid content analysis for biochemical and tumor markers can help to differentiate mucinous from nonmucinous tumors, preventing unnecessary pancreatic resection of benign lesions [78, 80]. The biochemical and tumor markers that can help in the diagnostic process are shown in Table 41.4.

Surgical Treatment

Most authors agree that the presence of a potentially resectable solid pancreatic mass in a CT scan or endoscopic US in an otherwise healthy patient, with no clinical or biochemical characteristics suggesting a benign condition such as autoimmune pancreatitis, should prompt us to offer surgical treatment. A proposed algorithm for the management of PI is shown in Fig. 41.1 [12]. Indications for biopsy are (a) a neoadjuvant chemotherapy protocol, (b) irresectability, (c) significant comorbidities that contraindicate a major surgical procedure, (d) undetermined diagnosis (inflammatory vs neoplastic), and (e) an apparently resectable lesion with suspicious lymph node enlargement.

The extent of surgery in patients with solid PI should be dictated by tumor location, number of lesions, and feasibility of establishing the diagnosis. If malignancy is confirmed or cannot be ruled out, a standard resection depending on the location of the PC should be performed (pancreatoduodenectomy or distal pancreatectomy). Enucleation or resection of ICT is performed depending on the location of the tumor and its relationship to the pancreatic duct; central pancreatectomy may also be considered in selected patients.

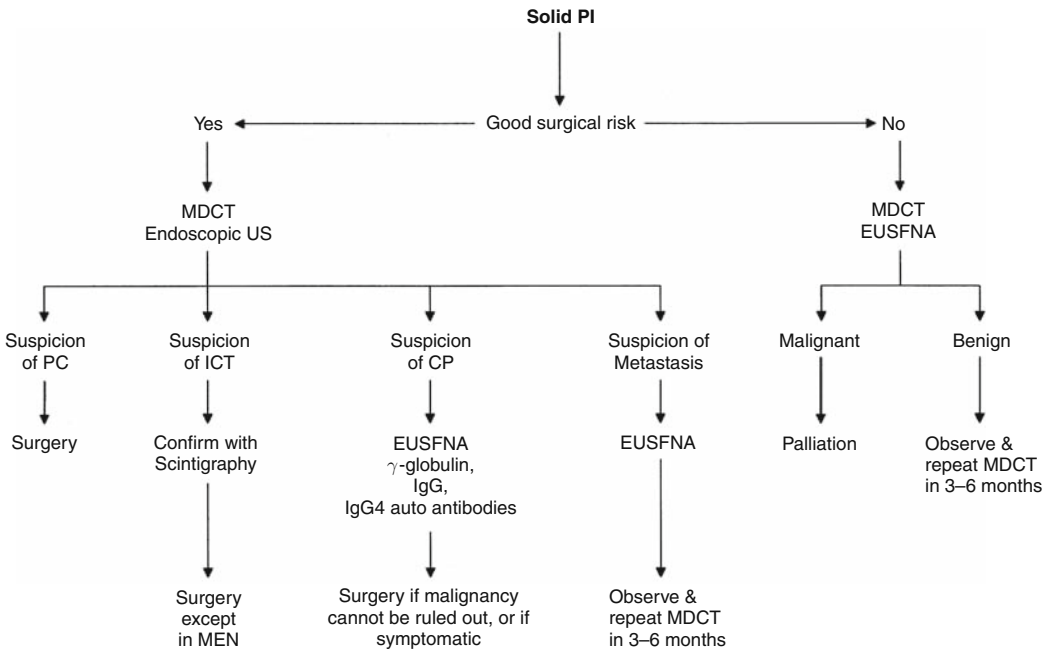

Fig. 41.1. Management algorithm for solid PI. CP: chronic pancreatitis; EUSFNA: endoscopic ultrasound-guided fine-needle aspiration; ICT: islet cell tumor; MDCT: multidetector row spiral CT scan; PC: pancreatic cancer; PI: pancreatic incidentaloma.

Some authors have advocated aggressive surgical treatment for pancreatic metastases, based on the fact that a reasonably good long-term survival can be achieved in some patients [52].

General rules for the management of cystic lesions are to resect potentially malignant tumors such as mucinous cystadenomas and intraductal papillary mucinous neoplasms and to observe benign lesions such as serous cystadenoma [80, 81]. Data from recent studies have confirmed the benign course of cystadenomas. Surgical treatment is then reserved for symptomatic lesions or for tumors with significant growth during follow-up. Allen and colleagues [59] reported symptoms in 35% of lesions with a mean diameter of 4.9 cm; whereas Tseng and colleagues described symptoms in 72% of patients with lesions >4 cm [82]. Resection has generally been recommended for tumors equal to or larger than 3 cm (Fig. 41.2).

In a series of 221 patients with cystic neoplasms [83], nonoperative treatment was offered to patients who were asymptomatic, older than 62 years of age, or had small cysts (median 2.4 cm). The majority of patients were followed by image studies (67%). After a mean follow-up of 24 months, 19% of the tumors demonstrated an increase in size. All resected lesions were benign.

Similarly, two studies from the Massachusetts General Hospital have recommended nonoperative management for patients with asymptomatic incidentally discovered cystic lesions <2 cm in size and in elderly patients with nonmucinous lesions with normal CEA levels on fluid analysis [57, 82]. The incidence of malignancy in patients with small lesions (<2 cm) who underwent resection was only 3% [57].

A study from the Memorial Sloan Kettering Cancer Center analyzed predictive factors for malignancy in PI [59]. The presence of a solid component in a mucinous cyst lesion was the most important predictive factor (61%); growth of a cystic lesion was also associated with malignancy.

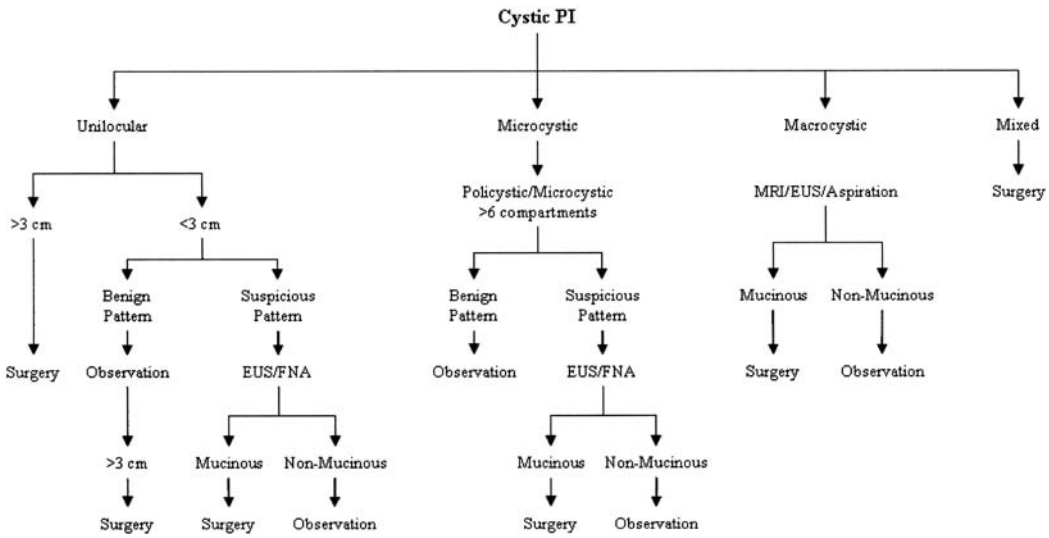

Fig. 41.2. Management algorithm for cystic PI. EUSFNA: endoscopic ultrasound-guided fine-needle aspiration; MRI: magnetic resonance imaging; EUS: endoscopic ultrasound.

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42

Technique of Pancreatic Resection

Laureano Fernández-Cruz

Introduction

Laparoscopic pancreatic resection was first introduced in 1994 by Gagner and Pomp [1] and Cushieri [2]. Using the criteria of Cushieri and Jakimowicz [3], the probable benefit of minimally invasive surgery over conventional open surgery depends on the ratio of access to procedural trauma. In pancreatoduodenectomy, the access trauma forms only a small component of the total operative insult to the patient. Therefore, laparoscopic approach is to be recommended only when its postoperative course can promise a better outcome than that of the current open approach. However, favorable postoperative results in terms of less pain, less analgesia requirement, early return of bowel function, and shorter hospital stay, in patients who underwent laparoscopic pancreatic resection for left-sided pancreatic lesions have been consistently reported [4–20]. The majority reports on laparoscopic pancreatic surgery (LPS) are often based on limited experience with short-term outcome. Recently, a multi-institutional European study (25 European Centers), including 127 patients, demonstrated that laparoscopic pancreatic resection is feasible and safe in selected groups of presumed benign pancreatic lesions requiring enucleation procedures or left-sided pancreatic resections [18]. A point of criticism of this study was that only four centers (16%) reported more than 10 patients.

Some authors have suggested that malignant pancreatic neoplasms are a contraindication to laparoscopic resection because of concerns on the lack of radicality of the resection and the inferior oncological outcomes [5]. However, we have recently demonstrated the feasibility, safety, and long-term outcome of the laparoscopic approach in 103 patients with benign, premalignant, and overt malignant lesions of the pancreas. To our knowledge, this is the largest single-institution series on this subject to date [21].

Techniques of Laparoscopic Distal Pancreatectomy Resection

Laparoscopic distal pancreatectomy (Lap DP) maybe performed with or without spleen preservation. When performing spleen-preserving distal pancreatectomy (Lap SPDP), this operation may be carried out with or without splenic vessels preservation (Warshaŵs technique). These techniques are frequently performed in patients with presumed benign pancreatic lesions. However, laparoscopic distal pancreatectomy with splenectomy (Lap SxDP) should be performed in patients with malignant tumors.

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Laparoscopic Surgery

Using one approach [7, 19, 20], the patient is placed in the half-lateral position with the left side up. The surgeon and the assistant stand on the left side of the patient and the camera person and scrub nurse on the opposite side. Four 10- to 12-mm trocars are inserted in the abdominal wall 3–4 cm above the umbilicus, on the xiphoid area, subcostal on the midaxillary line, and subcostal to the midclavicular line. Two monitors are used. CO_2 pneumoperitoneum is used. Abdominal pressure is monitored and maintained at below 14 mmHg. A 30° scope is used. The liver is explored visually and by laparoscopic ultrasonography (7.5 MHz probe, 10 mm diameter; B-K Medical, Gentolfe, Denmark) (Lap US).

Using another approach [21], the patient is placed in the Lloyd Davis position with the table tilted head up. The operating surgeon stands between the patient's legs, and two assistants stand on both sides of the patient.

Spleen-Preserving Distal Pancreatectomy with Splenic Vessels Preservation

Step 1: The first step is to start with sectioning the lienorenal ligament and dissecting the subjacent fascia lateral to the spleen. The splenocolic ligament is divided using a harmonic scalpel or Ligasure device. The splenic flexure of the colon is mobilized downward. The gastrocolic omentum is widely opened up to the level of the mesenteric vessels, and the body-tail of the pancreas is then visualized. The anterior aspect of the pancreas is exposed by dividing the adhesions between the posterior surface of the stomach and the pancreas. Care must be taken to preserve the short gastric and the left gastroepiploic vessels. Step 2: The inferior border of the pancreas is dissected and the body and tail of the pancreas are completely detached from the retroperitoneum. This mobilization of the left pancreas allows visualization of the posterior wall of the gland, where the splenic vein is easily identified. The splenic vein is pushed away from the posterior pancreatic wall by gentle blunt dissection. Visual magnification through the laparoscope permits excellent control of the small pancreatic veins, which are coagulated using the Ligasure device or the harmonic scalpel, or clipped with titanium clips (Figs. 42.1 and 42.2). A tunnel is created between the splenic vein and the pancreas. The splenic artery is identified through this space using blunt careful dissection with a curve dissector. Step 3: The pancreas is then transected with a 30-mm endoscopic linear stapler. Usually two stapler applications are necessary. Step 4: The tail of the pancreas is then grasped and retracted anteriorly with a 5-mm forceps, and traction is applied to expose the small branches of the splenic artery and vein, which are coagulated using the Ligasure device. The dissection is continued laterally until the splenic hilum. The vascular area connecting the end of the tail of the pancreas and the spleen is transected with a 30-mm endoscopic linear stapler (EndoGIA). Another option is to expose the vessels connecting the tail of the pancreas with the splenic vessel, which are ligated and coagulated.

Spleen-Preserving Distal Pancreatectomy Without Splenic Vessels Preservation

This technique follows the same surgical steps as described above until the plane behind the neck-body of the pancreas and the front of the

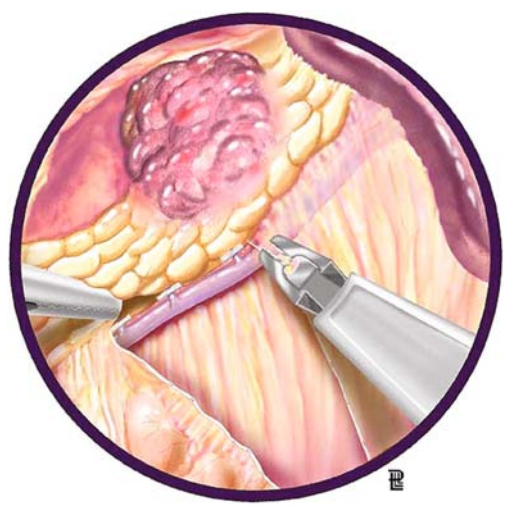

Fig. 42.1. Laparoscopic spleen-preserving distal pancreatectomy with splenic vessel preservation.

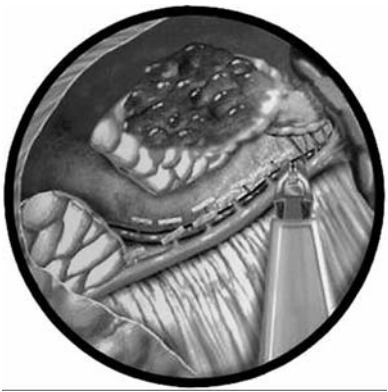

Fig. 42.2. The splenic vessels are preserved and the vascular attachments of the tail of the pancreas with the splenic hilum are clipped.

superior mesenteric and portal veins is reached. At this point the splenic vein is divided between clips (Step 1). The use of lapEUS demarcates the line of pancreatic transection 2 cm away from the tumor. Step 2: After pancreatic transection the splenic artery is divided between clips. Step 3: The left pancreas is then lifted up and mobilized posteriorly with the splenic artery and vein. The latter are clipped and divided or transected with endoGIA as they emerge from the pancreatic tail to enter the hilum of the spleen (Fig. 42.3). Step 4: The spleen is kept vascularized solely from the short gastric vessels and the left gastroepiploic vessels.

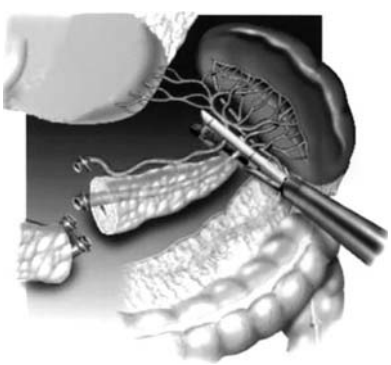

Fig. 42.3. Laparoscopic spleen-preserving distal pancreatectomy without splenic vessel preservation. Care should be taken when transecting the splenic vessels at the splenic hilum to preserve the short gastric vessels and gastro-epiploic vessels.

En-Bloc Laparoscopic Distal Pancreatectomy with Splenectomy

This operation (Lap Sx DP) should be performed in patients with suspected pancreatic malignancy and in patients with ductal adenocarcinoma of the body-tail of the pancreas. The principles of this operation follow the technique described by Strasberg et al. [22] in 2003, called radical antegrade modular pancreatosplenectomy (RAMPS). The technical details of this operation performed laparoscopically are as follows: Four ports are placed; a 10-mm port in the midline above the umbilicus for the laparoscope, 10-mm port in the left midclavicular line, 1–3 cm below the costal margin, 11-mm port in the left mid-axillary line below the costal margin, and 11-mm port in the right midclavicular line. The first step is to divide the lienorenal ligament and to dissect the adjacent fascia lateral to the spleen. The splenocolic ligament is divided using the harmonic scalpel. The splenic flexure of the colon is mobilized downward. The gastrocolic omentum is widely opened up to the level of the mesenteric vessels, and the body-tail of the pancreas is then visualized. The anterior aspect of the pancreas is exposed by dividing the adhesions between the posterior surface of the stomach and the pancreas. The omentum is opened to facilitate identification of the coeliac trunk and its branches to perform regional lymphadenectomy. Careful placement of a liver retractor creates a substantial working space. A grasping forceps is then passed behind the stomach from left to right to facilitate anterior and lateral retraction of the stomach. A large lymph node is usually present in the hepatoduodenal ligament and the hepatic artery can usually be found just cephalic to this. The common hepatic artery is then identified proximal and distal to the gastroduodenal artery; at this point the lymph nodes are mobilized. A complete dissection of the superior border of the pancreas in front of the common hepatic artery allows identification of the anterior surface of the portal vein. This maneuver is usually bloodless and the dissection is continued along the coeliac trunk to identify the left gastric artery and the splenic artery. Once the lymphadenectomy is completed around these vessels, the splenic artery is clipped (7 mm titanium clips) and divided 1–2 mm from its origin of the coeliac

trunk (Fig. 42.4). The inferior border of the pancreas is dissected and the body and tail of the pancreas are completely detached from the retroperitoneum. This mobilization of the left pancreas allows visualization of the posterior wall of the gland, where the splenic vein is easily identified. At this point the splenic vein is divided between 7 mm clips. The pancreas is then transected with a 30-mm endoscopic linear stapler; usually two stapler applications are necessary. The left pancreas is then lifted up and mobilized posteriorly with the splenic artery and vein. The lymph nodes along the superior border of the body and tail are mobilized. The dissection now proceeds to expose the anterior surface of the superior mesenteric artery; in this area the lymph nodes, fat, and fibrous tissue are taken. The dissection is continued posteriorly and the inferior attachments of the pancreas are divided. The inferior border of the pancreas is dissected including Gerota's fascia on the superior surface of the kidney; this dissection is continued anterior to the adrenal gland which is resected if invaded by tumor (Fig. 42.4). When pancreatosplenectomy is indicated, division of the lienorenal ligament and division of the short gastric vessels are the last step in the procedure. Table 42.1 describes the surgical steps using the laparoscopic approach for presumed benign lesions and for suspected or overt malignant lesions.

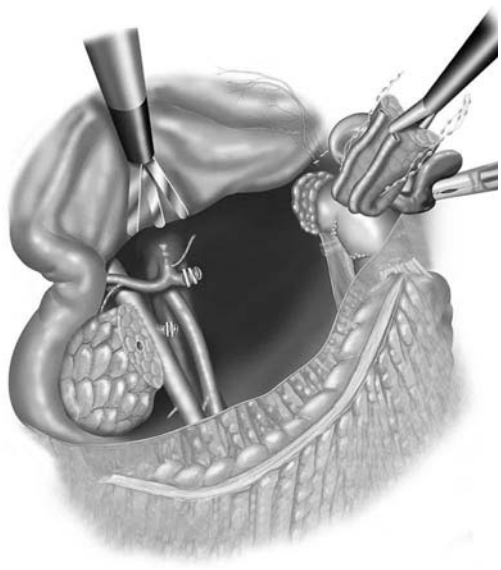

Fig. 42.4. Pancreatosplenectomy for suspected or malignant pancreatic tumors.

Outcome of Laparoscopic Distal Pancreatic Resection

In our recent series [21] the most common indications for LPS were benign-appearing pancreatic tumors, such as neuroendocrine neoplasms (41.7%). Other indications were cystic neoplasms of the pancreas, mainly mucinous cystic neoplasms (28.1%) and IPMN (9.7%) with premalignant or an overtly malignant tendency. Ductal adenocarcinoma represented 12.6% of the indications in this series and less common indications were left-sided chronic pancreatitis with inflammatory tumors (7.7%) [21].

LPS was feasible in 93% of the patients. Indications for conversion included technical problems, anatomical (occult tumor) or oncological features that precluded a safe laparoscopic approach. The most frequent technique used in this series was laparoscopic distal pancreatic resection (79.6%) but with splenic-salvage in 63.5% of cases.

Experience with LPS for patients with pancreatic neuroendocrine tumors (PNT) is still limited with short-term follow-up based on small series of patients or single case reports. In 1996 Gagner et al. reported the early experience with laparoscopic resection of islet cell tumors [23]. Since then, the experience worldwide is still limited and the majority of reports on LPS are often based on limited experience with short-term outcome. Assalia and Gagner [16] reported a review of the world literature dealing with laparoscopy of PNT using the Medline database covering the period January 1966 to October 2003. A total of 93 reported cases were found. The largest experience from the same institutions comprised no more than 10 patients. Insulinoma was the most prevalent diagnosis, comprising 87% of all cases. Other PNT were rare, with three gastrinomas (two of them metastatic and converted), one malignant vipoma (also converted), and seven unspecified "other," and nonfunctioning PNT [23]. The laparoscopic procedures performed were equally divided between laparoscopic distal pancreatectomy (Lap DP) and laparoscopic enucleation (Lap En) (39 cases each), with 15 converted cases (16.1%). In our recent report, LPS was feasible in 100% of 49 patients with

Table 42.1 Laparoscopic pancreatic resection: technical options

	Presumed Benign Lesions	Suspected or Malignant Lesions
Position of the patient	Half-lateral with the left side up	Lloyd Davis
Surgeon	On the left side of the patient	Between the patient's leg
Surgical Steps		
1	Division of splenocolic ligament Splenic flexure of the colon is mobilized downward Gastrocolic omentum is widely opened	
2	Inferior border of the pancreas dissected Body and tail of the pancreas completely detached from the retroperitoneum	
3	The splenic vein is visualized and clipped	Identification of celiac trunk and its branches
4	The pancreas is transected. The left pancreas is retracted anteriorly and traction is applied to expose the splenic artery	Lymphadenectomy in the areas of common hepatic artery, celiac artery, and left gastric artery
5	The splenic artery is clipped at its origin	The splenic artery is clipped at the origin
6	Preservation of the short gastric vessels	The neck of the pancreas is transected
7	Transection in the area between the tail of the pancreas and the hilum of the spleen	The splenic vein is clipped at its junction with the mesenteric vein
8	Preservation of the spleen	Lymphadenectomy on the superior border of the pancreas
9		Lymphadenectomy along the superior mesenteric artery
10		Fatty tissue, lymph nodes and nerves are removed between the posterior wall of the pancreas and the adrenal gland and left kidney. Adrenalectomy when adrenal invasion
11		The Gerotás fascia attached to the lateral border of the pancreas is removed
12		The short gastric vessels are coagulated and divided
13		Pancreatosplenectomy

PNT with benign tumors (77.5%) and malignant tumors (22.4%). We also have recently reported the outcome of the laparoscopic approach in patients with PNT [24].

Laparoscopic Surgery in Patients with Nonfunctioning PNT

Nonfunctional PNT are located most commonly (approximately 60%) in the pancreatic head but can be found anywhere within the pancreas. Generally, the diagnosis is often delayed (>5 years) and tumors become clinically apparent when already inoperable and/or metastatic. In patients with localized, nonmetastatic disease, complete surgical resection of the primary tumor is the treatment of choice [25–27]. The median survival was reported as 7.1 [28] years. However, only 48% of the patients with localized, nonmetastatic disease who underwent resection of the primary tumor were alive and without evidence of recurrent disease at a median follow-up of 2.7 years (range 1–8 years) from diagnosis [28]. The authors emphasized that complete resection of the primary tumor in the absence of metastatic disease should not

be assumed to represent long-term cure. Phan et al. [29] reported that the 5-year survival rate following resection approximated 50%.

In patients with metastatic disease, resection of the primary tumor should be based on the presence of clinical symptoms and the location of the tumor. In the absence of a symptomatic primary tumor with unresectable extrapancreatic metastatic disease, distal pancreatectomy is probably not indicated. In selected patients with localized liver metastases a combined resection of the primary tumor and liver metastases should be attempted [30–34]. The 5-year survival for patients who were cleared of pancreatic and liver disease was 65% in recent series [30]. However, tumor recurrence occurred in three quarters of patients who underwent resection with curative intent and most of these recurrences were detected within 2 years.

In our laparoscopic series the mean size of the nonfunctioning PNT was 5 cm. Patients with tumors $\leq$ 3 cm (6 patients) were managed with laparoscopic enucleation (Lap En) and local lymph node dissection to exclude metastatic lymph node involvement; benign tumors were the final diagnoses in this group [24]. Malignancy was found in 25% of nonfunctioning PNT cases but in 40% of cases when tumors were larger than 5 cm in size [24]. Ro laparoscopic resection was achieved in 100% of patients with malignant nonfunctioning PNT. Based on these results, nonfunctioning PNT $\leq$3 cm in size may be managed with an organ-preserving operation such as laparoscopic enucleation. In patients with tumors exceeding 5 cm in size, laparoscopic pancreatic resection should be an oncological resection (modified Strasberg's operation) including radical lymph node dissection of the peripancreatic, portal, hepatic, and superior mesenteric areas (Fig. 42.4). At a mean follow-up of 37 months (range 2–89 months) no patient with benign or low-grade malignancy had tumor recurrence but these preliminary data need confirmation [24]. However, patients with high-grade malignancies tend to recur. In a high-volume surgical series, the overall survival for PNT was 41 months and half of the patients developed metachronous liver metastases during observation [28].

Laparoscopic Surgery in Patients with Gastrinoma

The role of laparoscopy in the management of patients with gastrinoma is controversial. Recently, Norton and Jensen [35] have raised four reasons against a laparoscopic approach for gastrinoma: "First, gastrinomas are 3 to 10 times more common in the duodenum than the pancreas. Second, many gastrinomas are not localized preoperatively; especially duodenal gastrinomas, and this will likely decrease the success rate. Third, many gastrinomas, are associated with adjacent lymph node metastases. This will make a laparoscopic approach more difficult, prolong its duration, and may limit its success. Fourth, greater than 75% of gastrinomas are in the pancreatic head region in the so-called gastrinoma triangle, complicating the laparoscopic approach." These criticisms should be kept in mind before applying the laparoscopic approach, which may be feasible for selected cases. When the tumor is localized preoperatively in the pancreas, the feasibility of laparoscopic enucleation should be the same as in the cases of insulinomas, independent of whether the tumor is situated in the pancreatic head or in the body-tail. In patients with multiple tumors, especially MEN-1, when located in the body-tail of the pancreas, laparoscopic distal pancreatic resection is the same as for other PNT. The laparoscopic approach in duodenal gastrinoma should only be attempted when the tumor is localized preoperatively in the anterior duodenal wall to allow a safe excision. There is no question that lymph node dissection should be part of the laparoscopic approach at the time of tumor resection. The limits of the laparoscopic approach in patients with gastrinoma are reflected in our series with 4 patients [24]. Two patients were converted to open surgery. In one patient, the gastrinoma was situated (localized by Lap US) in a difficult surgical area, the posterior duodenal wall in proximity to the papilla of Vater. In another patient, the extracapsular nodule resected laparoscopically was doubtful to be a metastatic lymph node of a malignant duodenal or pancreatic gastrinoma. Pylorus-preserving pancreatoduodenectomy (open) was performed. The final pathological study was 0.4 mm pancreatic gastrinoma with metastatic lymph node. Two other patients were

successfully managed by laparoscopy [24]. The MEN-1 patient after Lap SPDP has been disease-free 2 years after surgery. One of our patients has been disease free 3 years after laparoscopic excision of primary lymph node gastrinoma. The diagnosis fitted into the definition "as occurring in a patient whose only extrahepatic tumor resected was in a lymph node and who was disease-free post-resection" (normal fasting serum gastrin levels, negative secretin tests, and no tumor on imaging studies). Norton et al. [36] reported 138 patients with sporadic ZES, 36 (26%) had only lymph nodes removed, and 22 patients (16%) were disease free immediately postresection. During follow-up, 16 patients (12%) remained cured. During this follow-up period, six patients relapsed and two had small duodenal primaries that were missed at the original exploration. These long-term cures strongly supported the conclusion that primary lymph node gastrinomas existed.

Laparoscopic Surgery in Patients with Vipoma

Vipomas account for less than 10% of NPT. They are much more common in women (with a female: male ratio of 3:1), and most frequently occur at around the fourth decade of life [37]. Up to 90% of ViPomas originate in the pancreas, and are usually solitary tumors. The majority of lesions are located in the distal pancreas. Over 60% of pancreatic ViPomas are malignant, and by the time of diagnosis up to 60% have metastasized to lymph nodes, liver, kidneys, or bone. The hypersecretion of VIP produces a syndrome characterized by severe secretory diarrhea, associated with hypokalemia and dehydration, and is commonly called the Verner–Morrison Syndrome. The diarrhea is intermittent in 53% of patients and continuous in 47%. Analysis of the Mayo Clinic data reported by Smith et al. showed that only 44% of patients with Vipomas were resectable, and only 28% of them were potentially curative. Long-term survivors are not uncommon; in the Mayo Clinic series the mean survival was 3.6 years, and the longest overall survival was 15 years [37]. Of the patients with resectable disease, the laparoscopic approach may be indicated when the tumor is localized in the body-tail of the pancreas. In our series [24], two patients are still alive 3 and 5 years after Lap SPDP and one patient after Lap SxDP is awaiting liver transplantation. Most of the published studies on liver transplantation in patients with PNT were retrospective and involved a limited number of patients; however, the data indicated that in otherwise healthy patients under the age of 50 years, hepatic transplantation might prolong symptom-free survival with acceptable operative morbidity [38, 39].

Laparoscopic Surgery in Patients with Glucagonoma

Glucagonomas are less than half as common as Vipomas, with an annual incidence of 0.01–0.1 new cases per million. They are slightly more common in women (55%) and usually occur after 45 years of age [40]. Most glucagonomas are large solitary tumors, which are almost exclusively found in the body or tail of the pancreas. The diagnosis is established by measuring the serum concentration of glucagon, with levels of $>$500–1000 pg/ml. The vast majority of glucagonomas are metastatic at the time of diagnosis [40]. However, due to the slow-growing nature of these tumors and the improvement in symptoms with resection, it is generally recommended that primary tumors without features of unresectability in preoperative imaging should undergo surgical removal of the primary tumor and resection of accessible hepatic metastases.

The Mayo Clinic published a 15-year experience with 21 patients with glucagonoma. Treatment consisted of surgical resection and debulking, chemotherapy, somatostatin analogues, and hepatic embolization, resulting in significant palliation of symptoms. In addition, despite the presence of metastatic disease in all 21 patients at the time of diagnosis, only 9 died of their disease over 5 years of follow-up [40, 41]. For patients who were not candidates for surgical resection or for those who developed recurrent disease, somatostatin or its analogues were generally effective in controlling clinical symptoms. In our series [24] of one patient with glucagonoma, diffuse liver metastases developed 4 years after successful Lap SPDP, but remained asymptomatic.

Laparoscopic Surgery in Patients with Carcinoid Tumors

Carcinoid tumors are defined as tumors with neuroendocrine histological features and evidence of serotonin production. The overall incidence of these tumors is approximately 1–2 cases per 100,000 populations. In all reported series, the majority of the cases are of midgut origin, with a relatively small percentage arising in the foregut organs. Pancreatic carcinoids have a poorer outcome than other foregut carcinoids, perhaps because of their location and tendency to produce relatively nonspecific symptoms resulting in more advanced tumors at presentation. In fact, pancreatic carcinoids were universally metastatic at diagnosis [42, 43]. Hindgut and foregut other than pancreatic carcinoids had the most favorable prognoses (46% 10-year survival for rectum, 62% 10-year survival for duodenum, 56% 10-year survival for stomach). Pancreatic carcinoids had the poorest prognosis, with 10% alive at 10 years. A major question is whether or not aggressive surgery to resect metastatic tumors will result in prolonged survival. Some suggested that resection of metastatic carcinoid tumor in liver could be markedly beneficial or curative in selected patients [44]. In our series, two patients after Lap SxDP and liver resection for metastatic disease were disease-free [24] although the follow-up was relatively short.

Laparoscopic Surgery in MEN-1 Patients with Insulinomas

The role of surgery in patients with insulinomas associated with MEN-1 has been defined by Demeure et al. [45] in a review of the literature comprising 60 patients. The authors suggested that patients with insulinomas associated with MEN-1 needed a different surgical approach from those with sporadic tumors. In most reports, enucleation or limited resection did not result in the development of recurrent hyperinsulinism up to 15 years although others reported recurrence rates of up to 40% at 10 years after enucleation [46–48]. Enucleation of an insulinoma alone in patients with MEN-1 would likely lead to missed tumors and failed operation [46]. More than 75% of patients with insulinoma associated with MEN-1 had multiple pancreatic tumors. Subtotal distal pancreatectomy with spleen preservation and combined with enucleation of any tumors identified in the pancreatic head should be the standard operation. We believe that patients with MEN-1 insulinomas may benefit from the choice of the laparoscopic approach according to the principles developed during the past 20 years from the standard open approach [46–48]. During surgery, intraoperative Lap US may identify other tumors not seen in preoperative localization studies. In addition, Lap US identifies the demarcation between normal pancreas and macroscopic disease and is useful for determining the optimal site of transection. In our series two MEN-1 patients with hyperinsulinism underwent Lap SPDP and remain asymptomatic and normoglycemic at 40 and 44 months [15, 24].

Laparoscopic Surgery in MEN-1 Patients with Zollinger–Ellison Syndrome

The role of surgery for MEN-1 Zollinger–Ellison syndrome (ZES) patients is debatable [48–51]. In MEN-1 patients with ZES, 70–95% of primary tumors arise in the duodenum and 30–25% in the pancreas. Äkerstrom et al. [52] have advocated excision of duodenal gastrinomas, enucleation of possible tumors in the head of the pancreas, regional lymphadenectomy, and distal pancreatic resection (as an intent to resect nonfunctioning tumors and reduce the risk of recurrence) However, Cadiot et al. [53] reported that the only independent factor associated with the development of liver metastasis was a pancreatic primary tumor larger than 3 cm in MEN-1 patients with ZES. According to these results, surgery should be performed for patients with tumors >3 cm or when excess gastrin could be localized. The reason for this discrepancy is that biochemical relapse occurs in more than 95% of patients 3–5 years after surgery, but can be associated with an excellent prognosis [54]. Several reports have shown a 62–87% and 47–77% 5- and 10-year survival rates respectively for all

ZES patients [54–56]. One of our patients with ZES associated with MEN-1 had MEN-2 tumors (2 and 1.5 cm) localized in the body-tail of the pancreas [24]. In addition, abdominal pain and dilatation >5 mm of the duct of Wirsung in the tail of the pancreas were present. Lap SPDP was performed, and there was a clear obstruction of the duct of Wirsung by one the tumors in the pathological specimen. This patient is clinically cured 2 years after surgery [24].

Laparoscopic Surgery in Patients with Sporadic Insulinoma

Surgical resection is the treatment of choice and offers the only chance of cure. The surgical strategy in patients with sporadic insulinoma should be restricted to removal of the solitary tumor in about 90% of patients. The use of enucleation or resection will depend on the location of the tumor in the pancreas and intraoperative ultrasonography (IOUS) findings. Laparoscopy and Lap US provide information similar to that obtained by means of open IOUS and can identify lesions that are undetectable by preoperative imaging techniques. Despite the advantages of Lap US, preoperative imaging is still worthwhile to provide useful information for patient positioning and port placement. Lap US also facilitates operative decision-making. Islet cell tumors are typically hypoechoic and easy to differentiate from the surrounding pancreatic parenchyma. This information helps the surgeon choose between enucleation (in an attempt to preserve healthy pancreatic parenchyma) or resection. Lap US is also essential in Lap En to choose between an anterior or a posterior surgical approach. In addition, Lap US can be of great assistance in guiding the enucleation procedure by avoiding injury to the pancreatic duct or large blood vessels. In cases of Lap DP, Lap US identifies the demarcation of the tumor from the normal pancreatic tissues and is useful for determining the optimal site of transection.

We have recently reported guidelines for laparoscopic surgical strategies in the management of insulinomas [57]. The reported success for laparoscopic resection of insulinoma ranges from 60 to 100% [11–15, 21, 58–60] . In our series, 20 patients had benign insulinoma; 9 localized in the head-neck of the pancreas and 11 in the body-tail of the pancreas [24]. One patient was converted to open surgery and enucleation was performed. Lap En and Lap SPDP was performed in 15 (79%) and 4 (21%), respectively [24]. The percentage of enucleation by laparoscopic surgery in this series compares favorably with other large series using the open approach [61].

Conversion to Open Surgery

In the literature, conversion rates range from 20 to 33% [59]. In our recent report 4/49 (8.2%) patients were converted to open surgery [24]. None of the patients with nonfunctioning tumors were converted. Among the functioning tumors, conversion rate was highest in patients with gastrinoma (50%) and the lowest in patients with sporadic insulinoma (4.8%) [24].

Conclusions

The open distal pancreatic resection has a long, proven track record of providing a cure for PNT with acceptable morbidity and mortality. Laparoscopic distal pancreatic resection is a complex advanced laparoscopic operation that accomplishes the same objectives as open distal pancreatic resection but avoids major access trauma. The method of access and exposure for laparoscopic approach should result in less surgical insult compared with open surgery. Laparoscopic spleen-preserving distal pancreatectomy with or without splenic vessel preservation is feasible and can be achieved in most cases. Laparoscopic en bloc splenopancreatectomy using a modified RAMPS procedure can achieve negative tangential margins in a high percent of patients with resectable malignant neuroendocrine tumors of the body and tail of the pancreas. The reduced incidences of wound infection and late incisional hernia, and enhanced recovery with reference to time to return to daily activities after laparoscopic distal pancreatic resection are all recognized advantages of this surgical approach.

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Section V
Familial Endocrine Conditions

43

Familial Endocrine Conditions

Oliver Gimm

Introduction

Endocrine diseases most commonly occur in a sporadic manner but may have a hereditary background and be part of a complex syndrome. A variety of familial endocrine conditions exist such as the Carney complex [1], the Cowden syndrome [2], the von Hippel-Lindau syndrome [3], the hyperparathyroidism-jaw tumor syndrome [4], and the pheochromocytoma–paraganglioma syndrome [5] (Table 43.1).

For the surgeon, a knowledge of these syndromes is very important. For example, (1) patients with multiple endocrine neoplasia (MEN) 1-related gastrinoma often also have primary hyperparathyroidism which should be treated first because hypercalcemia increases gastrin secretion. (2) Patients with MEN 2-related medullary thyroid carcinoma (MTC) may also develop pheochromocytoma (almost always benign) that must be treated first in order to prevent an intraoperative hypertensive crisis.

This chapter focuses on genetic and clinical aspects of MEN 1 and MEN 2.

Multiple Endocrine Neoplasia Type 1

Genetic Aspects

MEN 1 has an autosomal dominant pattern of inheritance which was first described by Wermer in 1954 [6]. In 1997, the gene (*MEN1*) causing MEN 1 was identified [7]. The *MEN1* gene is localized on chromosome 11q13 and consists of 10 exons. Today, *MEN1* germline mutations are found in about 90% of patients with MEN 1. Mutations in the *MEN1* gene do not appear to cluster in hot spots. Truncating frameshift and nonsense mutations are most common (about 60%), although other mutations including missense, deletions, insertions, and splice-site mutations are found.

Genotype–Phenotype Correlation

To date, no clear genotype–phenotype correlation has been found. The exception may be specific missense mutations that have been identified in familial isolated hyperparathyroidism (FIHP) [8, 9]. Some authors report nonsense mutations to be associated to gastro-entero-pancreatic (GEP) and carcinoids of the lungs and thymus [10]. Modifier genes and/or environmental factors may explain the variable penetrance of the various MEN 1-related tumors even within one family harboring the same mutation.

MEN 1 Kindred Without MEN1 Mutation

Since about 90% of all patients with MEN 1 harbor a germline *MEN1* mutation, being confronted with an MEN 1 kindred without *MEN1* mutations has become a rare event. In these cases, biochemical screening has to be performed as in the pre-*MEN1* era [11].

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Table 43.1. Familial endocrine conditions

Organ	Syndrome	Disease	Gene/ Chromosome
Thyroid	Cowden disease	Goiter, follicular thyroid carcinoma	*PTEN*
	Familial non-MTC	Papillary thyroid carcinoma (90%)	2q21
	Gardner	Papillary thyroid carcinoma	*APC*
	Hereditary hyperthyroidism	Goiter, hyperthyroidism	*TSHR*
	Hereditary hypothyroidism	Hypothyroidism	*TPO*, *NIS*, *TG*
	Multiple endocrine neoplasia type 2	Medullary thyroid carcinoma (MTC)	*RET*
	Pendred	Goiter, hypothyroidism	*PDS*
Parathyroid	Familial hypercalcemic hypocalcuria	Hyperparathyroidism	*CaSR*
	Hyperparathyroidism-jaw tumor	Hyperparathyroidism, parathyroid carcinoma	*HRPT2*
	Multiple endocrine neoplasia type 1	Hyperparathyroidism	*MEN1*
	Multiple endocrine neoplasia type 2	Hyperparathyroidism	*RET*
Adrenal	Beckwith-Wiedemann	Adrenal cortical carcinoma	*IGF2*, *H19*
	Carney's complex	Hypercortisolism (Cushing)	*PRKAR1A*, 2p16
	Familial paraganglioma-pheochromocytoma	Pheochromocytoma	*SDHB*, *SDHD*
	Gardner	Adrenal cortical carcinoma	*APC*
	Li-Fraumeni type 1	Adrenal cortical carcinoma	*p53*
	Multiple endocrine neoplasia type 1	Adrenal cortical adenoma	*MEN1*
	Multiple endocrine neoplasia type 2	Pheochromocytoma	*RET*
	Neurofibromatosis type 1	Pheochromocytoma	*NF1*
	von Hippel-Lindau	Pheochromocytoma	*VHL*
Pancreas, GIT	Beckwith-Wiedemann	Nesidioblastosis, Pancreatoblastoma	*IGF2*, *H19*
	Familial hyperinsulinism	Hyperinsulinism	*SUR1*
	Neurofibromatosis type 1	Duodenal carcinoids	*NF1*
	von Hippel-Lindau	Islet cell tumors	*VHL*

GIT – gastrointestinal tract

Screening

Apart from some lesions (e.g., gastrinomas, thymic carcinoids) that may be MEN 1-related in more than 20–25%, the percentage of patients having one MEN 1-related endocrine tumor and actually having a germline *MEN1* mutation is low. Thus, the questions of who should be screened for an *MEN1* mutation is a difficult one (Table 43.2). In general an *MEN1* mutation analysis is recommended for index patients, and, when a mutation is found, first-degree, and subsequent relatives.

The age at which clinical screening should be started in *MEN1*-mutation carriers remains a matter of debate but since 50% of the patients have developed pHPT by the age of 20, early investigation appears reasonable (Table 43.3). Various guidelines have been published [10, 12, 13].

Clinical Aspects

The prevalence of MEN 1 has been estimated to be about 1/20,000–40,000. MEN 1 is characterized by the coexistence of various endocrine disorders

Table 43.2. Indications for genetic screening for MEN 1

- At risk family members in known MEN 1 families
- Young patients (<50 years) with multiglandular or recurrent pHPT
- Patients with prolactinomas (ca. 15% MEN 1)
- Patients with multiple pancreatic endocrine tumors
- Patients with any MEN 1-related lesion and an adrenal lesion
- Patients with thymic or bronchial carcinoids

Table 43.3. Screening recommendations for MEN 1-related tumors in *MEN 1*-mutation carriers

Organ–Disease	Age (years)	Biochemical investigation (at least annually)	Imaging techniques (every 3–5 years)
Parathyroid			
–pHPT	10	Calcium (ionized), (intact) Parathormone	None
Pancreas			
–Insulinoma	5	Insulin, fasting glucose	None, unless biochemically diagnosed
–Gastrinoma	20	Gastrin, stimulated gastrin	None, unless biochemically diagnosed
–Other Gastro-enteropancreatic tumors	20	Chromogranin A, proinsulin, glucagon, pancreatic polypeptide	Endoscopic ultrasonography, (computed tomography, magnetic resonance imaging, octreotide scan)
Foregut			
–carcinoid	20	Serotonin, 5-HIAA	Computed tomography, magnetic resonance imaging, octreotid scan
–Thymic carcinoid	20–25	Serotonin	Computed tomography, magnetic resonance imaging, octreotid scan

involving the pituitary gland (adenoma), the parathyroid glands (hyperparathyroidism), and gastroenteropancreatic tumors (nonfunctioning, gastrinoma, insulinoma). Adrenal tumors and carcinoids (bronchial, thymus, foregut) may also be found. For most MEN 1-related diseases, the female to male ratio is roughly 1:1.

Hyperparathyroidism

The penetrance of hyperparathyroidism is very high. By the age of 20 years, more than 40% of patients develop pHPT, and by the age of 50, more than 90–95% have developed pHPT. Most patients present with a multiglandular disorder, but parathyroid carcinoma is almost never observed. The typical symptoms of "moans, groans, and stones" are rarely observed, and more commonly patients are identified through biochemical screening due to a family history. Surgery should be performed if the patients fulfil the biochemical criteria of pHPT, independent of clinical symptoms.

Gastroenteropancreatic Tumors

Gastroenteropancreatic endocrine tumors occur in 30–75% of patients with MEN 1. Their clinical expression is very variable.

Nonfunctional tumors account for the majority of pancreatic islet cell tumors in MEN 1 [14, 15]. These tumors are characterized by the absence of symptoms related to hormone hypersecretion. Of note, these tumors may still have in situ production of hormones [16] and/or may produce hormones without biological effects [e.g., neuron-specific enolase (NSE)].

The most common functional tumors are gastrinomas (50–60%) and insulinomas (20–30%). Glucagonomas (causing necrolytic migratory erythema and diabetes mellitus secondary to hyperglucagonism), VIPomas [causing watery diarrhea, hypokalemia, and achlorhydria (WDHA)] and other pancreatic endocrine tumors develop in less than 5% of MEN 1 patients.

Gastrinoma

Zollinger–Ellison syndrome (ZES) is the most common (50–60%) clinical manifestation of functioning gastroenteropancreatic endocrine tumors in MEN 1. It is caused by excessive production of gastrin by tumor cells. In more than 95% of patients the source of gastrin production is multiple duodenal tumors. The symptoms of peptic ulcers and diarrhea are caused by gastric acid hypersecretion. Up to 80% of the patients develop abdominal pain and esophageal reflux disease. Diarrhea occurs in about 10–20%. Multiple peptic ulcers or ulcers in atypical locations should suggest the diagnosis of ZES. Proton pump inhibitors (PPI) have significantly reduced the frequency of

severe complications such as bleeding, perforation and esophageal stricture.

Insulinoma

About 20–30% of all MEN 1 patients develop an insulinoma, while 5–10% of all patients with insulinoma have a background of MEN 1 [17]. Symptoms are caused by hyperinsulinism, inducing hypoglycemia and a subsequent catecholamine response. The list of differential diagnoses, however, is long and includes alcohol abuse, drugs, liver diseases, and enzyme/hormone/substrate deficiencies/defects and iatrogenic hyperinsulinism. In the sporadic setting, the diagnosis is not uncommonly made until years after the appearance of initial symptoms; however, the diagnosis is usually made earlier when the background of MEN 1 is known as the physician is aware of its potential development.

Adrenal Lesion

Adrenocortical lesions are found in 20–40% of patients. Frequently, these lesions are bilateral, nonfunctioning, and almost always benign [18, 19]. In rare cases, hyperaldosteronism (Conn syndrome) or hypercortisolism (Cushing's syndrome) have been reported.

Lesions of the adrenal medulla (pheochromocytoma) are rare, occurring in 2–3% [20].

Gastric ECLoma

ECLomas are believed to originate from the enterochromaffin-like (ECL) cells in the gastric mucosa. Gastric ECLomas are found in about 10% of patients. They almost never cause symptoms.

Thymic Lesions

Thymic carcinoids are rare (3–8%) in MEN 1, but among all patients with thymic carcinoids, ~25% are MEN 1-related [21]. Tumor development before the age of 30 appears to be a rare event [21]. About 90% of patients who develop thymic carcinoids have truncating *MEN1* mutations [22]. There is a male predominance (4:1), the reason for which is unclear.

These tumors are insidious, i.e., local invasion, recurrence, and distant metastases are frequently observed with no known effective treatment. Symptoms are caused due to local tumor expansion (pain, cough, hoarseness, venous compression), but about one third may remain asymptomatic [23].

Diagnosis and Imaging

Hyperparathyroidism

Biochemical screening for pHPT should start by the age of 10 at the latest and then be continued for life on an annual basis (Table 43.3). Once parathyroid hormone is elevated, surgery should be considered according to the recommendations given below. Preoperative imaging techniques are not necessary prior to primary surgery.

Gastroenteropancreatic Tumors

For islet cell tumors, annual screening starting at the age of 20 should include as a minimum fasting and secretin-stimulated gastrin levels (Table 43.3). The routine measurement of fasting glucose, insulin, glucagon, pancreatic polypeptide (PP), and chromogranin-A has also been advocated [11]. False-positive results due to hypertension, inflammatory bowel disease, and renal disease have been reported.

Due to the fact that a high proportion of tumors will be nonfunctioning, endoscopic ultrasonography [24] and abdominal imaging [e.g., computed tomography (CT)/magnetic resonance imaging (MRI) and octreotide scintigraphy] should be performed every 3–5 years. Endoscopic ultrasonography seems to be the preferred method [25].

Gastrinoma

Biochemical diagnosis of gastrinoma includes measurement of fasting gastrin levels, measurement of gastric pH, and gastrin provocative tests (e.g., secretin). Serum gastrin levels >1,000 pg/ml and gastric pH < 2 are considered diagnostic for gastrinoma. Otherwise, provocative tests may be required. Still, about 15% of the patients have negative tests. The important differential diagnosis is atrophic gastritis (high serum gastrin levels without gastric acid).

Percutaneous and endoscopic ultrasound, spiral CT, and MRI as well as somatostatin receptor scintigraphy can be used to localize the tumor. In most instances, however, the small multiple duodenal tumors cannot be found preoperatively. While selective arterial secretin injection (SASI) has been shown to be a useful diagnostic tool in the sporadic setting [26], its value in

MEN 1-related gastrinoma is not clear. The usefulness of positron emission tomography needs to be further evaluated [27]. In the absence of positive imaging techniques, patients should be liberally submitted to surgery since most of these patients have resectable duodenal lesions.

Insulinoma

Screening for insulinoma has been recommended to commence from the age of 5 [13]. Measurements of inadequate high insulin levels during times of low glucose levels are most often diagnostic. Whipple set forth the triad that bears his name: (1) signs and symptoms of hypoglycemia, (2) blood glucose levels below 45 mg/dl, and (3) relief of symptoms after glucose administration [28]. The fasting test is still considered the "gold standard" of testing. Measurement of proinsulin and C peptide may be additional helpful diagnostic tools. In addition to preoperative transabdominal and endoscopic ultrasound as well as spiral CT and MRI, selective arterial calcium injection (SACI) [29, 30] may be helpful in localizing and regionalizing the tumor that is almost exclusively found in the pancreas. The value of somatostatin scintigraphy is of minor value [31], since somatostatin receptors are expressed only in a minority of insulinomas [32].

Adrenal Lesion

No clear recommendations regarding screening are given. CT and MRI are most likely to detect the tumors.

Gastric ECLoma

Usually, these lesions are diagnosed during endoscopy for MEN 1-related ZES.

Thymic Carcinoids

CT or MRI and octreotide scintigraphy should be considered.

Therapy and Prognosis

Hyperparathyroidism

Almost all patients have multiglandular disease, and consequently partial parathyroidectomy results in a high rate of recurrence [33]. Thus, all parathyroid glands should be visualized. A remnant the size of half a normal parathyroid should be preserved, and the other three 1/2 glands are excised. When all the parathyroids are enlarged, a part of the smallest gland should be preserved. Whether to leave the preserved part in situ (subtotal parathyroidectomy) or to autotransplant it (total parathyroidectomy) is part of ongoing discussion [34].

Preservation without autotransplantation may give a lower risk of postoperative hypocalcemia [35] but leaves parathyroid tissue in the neck, which could make revisional surgery more cumbersome. When parathyroid tissue is preserved in situ, it should be marked with a nonabsorbable suture or a clip. Whether the parathyroid tissue is autotransplanted in the neck (e.g., sternocleidoid muscle) or the forearm (e.g., brachiocephalic muscle) is part of ongoing controversy. Autotransplantation to the brachiocephalic muscle creates a new wound but has the theoretical advantage in the case of recurrent disease due to the remnant of avoiding reoperative neck surgery. The autotransplanted parathyroid tissue is cut into small pieces and then placed individually into muscle pockets. The location should be marked as described above. A cervical thymectomy must be performed since up to 20% of patients harbor an intrathymic parathyroid tissue. This may also prevent the development of often malignant thymic carcinoids. It is reasonable to cryopreserve parathyroid tissue for autotransplantation at a later time should the parathyroid remnant not function properly.

Parathyroid carcinoma is almost never seen [36]. However, due to the genetic background, recurrence in the parathyroid remnant or rest of parathyroid tissue within the neck is a common event [37].

Gastroenteropancreatic Tumors

Apart from insulinoma, the prognosis of endocrine gastroenteropancreatic tumors is often determined by the high malignant potential of the tumors (glucagonoma >70%, VIPoma >40%, nonfunctioning tumors >70%).

This is the rationale to advocate an aggressive surgical approach, since other therapeutic options are limited [38]. A thorough investigation of the abdomen is mandatory in order to determine the extent of the disease and to identify liver metastases. The entire pancreas must be examined by palpation. In addition,

intraoperative ultrasound should be used to identify all lesions. In general, enucleation and/or partial resection is rarely indicated with subtotal (80–85%) (distal) pancreatectomy with enucleation of pancreatic head tumors being preferred, although pancreatoduodenectomy may be necessary in patients with large head or duodenal tumors [39, 40]. This procedure should not be done routinely since it implies difficulties of further treatment. Due to the hepatico-jejunostomy, liver metastases cannot be treated with embolization because of the risk of ascending infection.

Overall, patients with MEN 1-related gastroenteropancreatic tumors are considered to have a more favorable prognosis than sporadic counterparts. This may be due to the earlier diagnosis as a result of screening procedures. However, pancreatic malignancy is the most common cause of tumor-related death in MEN 1.

Gastrinoma

If MEN 1-related ZES is diagnosed, the copresence of pHPT should be ruled out since hypercalcemia increases gastrin secretion. If copresent, pHPT should be treated first. The hormonal excess of gastrinoma can nowadays be successfully treated with PPI, but this therapeutic approach does not prevent malignant transformation and subsequent metastatic disease and, hence, surgery is advocated whenever possible [41].

The abdomen should be thoroughly explored. In particular, the liver should be carefully investigated for the presence of metastases both by palpation and by ultrasound. To enable bimanual palpation of the pancreatic body and tail, the lesser sac should be opened. A Kocher maneuver facilitates inspection and palpation of the pancreatic head. To identify duodenal tumors, the most common (>95%) location of gastrinomas in MEN 1, a duodenotomy may be necessary. Since lymph node involvement is not uncommon, lymph node dissection is mandatory. One procedure that has often been recommended in patients with MEN 1-related ZES is splenic preserving distal pancreatectomy (resecting 80%), enucleation of pancreatic head tumors, exploratory duodenotomy, and lymphadenectomy [42]. A pancreas-sparing duodenectomy may be best for patients with a large duodenal tumor burden. Pancreatoduodenectomy may be performed in those patients having extensive duodenal and pancreatic tumor. Total pancreatectomy may be reserved to patients with large malignant tumors.

More than 40–50% of MEN 1-related gastrinomas are considered malignant. Up to 25% of the patients eventually develop liver metastases. However, less than 20% of these tumors demonstrate an aggressive behavior. Although there is a correlation between primary tumor size and metastatic potential, even the smallest tumors may metastasize.

Insulinoma

If required preoperatively, insulinoma may be treated with diazoxide, which lowers insulin secretion and subsequently raises glucose levels. Most insulinomas (75–95%) can be palpated. The use of intraoperative ultrasound is of major value, not only to localize the tumor itself (which is often hypoechoic) but also to identify its relation to the pancreatic duct and major vessels. In some instances, the tumor may be enucleated or resected performing a distal pancreatectomy. In contrast to sporadic insulinoma, however, the coexistence of other pancreatic tumors may require a more complex procedure in MEN 1 patients. The intraoperative measurement of insulin may be a helpful aid to demonstrate success intraoperatively [29, 43].

Insulinomas are malignant in only 5–10%, and the prognosis in this regard is very good. Recurrence in the pancreatic remnant, however, is possible due to the genetic background.

Adrenal Lesion

Most investigators recommend surgery once the adrenal lesion is 3 cm or larger. Due to the likelihood that both adrenal glands may be involved and the fact that malignancy is almost never seen, subtotal adrenalectomy is recommended when technically possible and lesions are nonfunctional. Since most lesions are benign, the prognosis is generally excellent. Due to the genetic background, recurrence may occur in the adrenal remnant.

Gastric ECLoma

ECLomas less than 1 cm in size may be treated by endoscopic polypectomy. Surgical excision may be performed in selected cases. It has been

reported that MEN 1-related ECLomas regress after surgical removal of gastrinomas [44].

The prognosis is considered to be excellent. Metastasis is a rare event, and death due to ECLomas is exceptional.

Thymic Lesions

Due to the risk of developing malignant thymic carcinoid, a prophylactic thymectomy may be considered at the age of 20–25 years. This is one reason why some investigators recommend performing a cervical thymectomy when operating on patients with primary hyperparathyroidism. However, malignant thymic carcinoids have been reported after transcervical thymectomy in MEN 1 [45].

Follow-Up

Due to the inability to predict tumor penetrance and malignant transformation on an individual basis, lifelong follow-up is recommended for MEN 1 carriers [46].

Hyperparathyroidism

Follow-up should include measurement of (intact) parathyroid hormone and (ionized) calcium at least annually. Recurrence after surgery for pHPT after subtotal parathyroidectomy have been reported in most studies between 5 and 20% and may be due to either the parathyroid remnant or supernumerary parathyroid glands. Thus, in the case of recurrent/persistent disease after primary surgery, operative and pathology reports of previous surgery should be reviewed. Localization studies are used to tailor the surgical approach. Options include technetium 99m sestamibi scintigraphy [47], methionine PET [48], selective venous sampling, supported by ultrasound, and/or CT/MRI. In the case of autotransplanted tissue into the forearm, the easiest diagnostic procedure is the Casanova test [49]. When possible a focused approach is used. While early PTH levels are often within the normal range, re-recurrence is commonly observed (20–70%) [50].

Gastrinoma

Depending on the stage of the disease and the procedure performed, roughly 50% of the patients may become eugastrinemic. The long-term outcome, however, remains uncertain and many patients develop recurrence. Measurement of basal and provoked gastrin levels may be performed postoperatively at 3-month intervals for the first year and individually determined longer intervals thereafter. Imaging techniques may be performed if the serum gastrin levels rise or become pathologic.

Insulinoma

Measurement of fasting glucose levels and insulin may be performed postoperatively and at least annually thereafter. Some authors consider SACI an essential imaging technique in reoperative cases.

Adrenal Tumors

Since contralateral tumor development or, in the case of subtotal adrenalectomy, ipsilateral tumor recurrence may occur, routine lifelong follow-up is mandatory.

Thymic Lesions

No clear recommendations have been given but lifelong follow-up is required.

Multiple Endocrine Neoplasia Type 2

Genetic Aspects

MEN 2 has an autosomal dominant pattern of inheritance and is caused by germline mutations of the proto-oncogene *RET* [51]. First described in 1993, *RET* is localized on chromosome 10q11.2 and consists of 21 exons. *RET* germline mutations are found in more than 98% of all patients with MEN 2, i.e., only a minority of patients that fulfil the clinical diagnosis of MEN 2 do not have a germline *RET* mutation. In these patients, the underlying cause is not known. The mutations found are almost exclusively missense mutations causing activation of RET. These mutations are found in hot spots affecting exon 8, 10, 11, 13, 14, 15, and 16.

Genotype–Phenotype Correlation

In patients with MEN 2A (see below), most mutations (>70%) are found in codon 634 (exon 11) [52].

In patients with MEN 2B (see below), almost all mutations (>95%) are found in codon 918 (exon 16) [53, 54].

Germline mutations of the extracellular coding domain of *RET* (codons 533, 609, 611, 618, 620, 634) are strongly associated with the presence of pheochromocytoma and/or hyperparathyroidism and, hence, most often found in patients with MEN 2A. Patients with familial MTC (FMTC) may have the same germline mutations in the same codons. Often, these patients have germline mutations in the intracellular coding domain of *RET* (codons 768, 777, 790, 791, 804, 844, 891, 912). Even though pheochromocytoma have not been described in all cases, the presence of a germline *RET* mutations in the latter codons, however, does not exclude the presence of MEN 2A. Hence, any patient with a germline *RET* mutation associated with hereditary MTC should be screened for the presence of pheochromocytoma and hyperparathyroidism (Table 43.4).

Table 43.4. Genotype-phenotype correlation in MEN 2/ FMTC

Exon	Codon	FMTC	MEN 2A	MEN 2B
8	533	533	533	
10	609	609	609	
	611	611	611	
	618	618	618	
	620	620	620	
11	630	630	630	
	634	634	634	
13	768	768		
	777	777		
	790	790	790	
	791	791	791	
14	804	804	804	804[a]
	844	844		
15	883			883
	891	891	891	
16	912	912		
	918			918
Mean age at diagnosis[b] (y)		45–55	25–35	10–20
MTC		90–100%[c]	90–100%[c]	100%
Pheochromocytoma		–	40–60%	40–60%
Primary hyperparathyroidism		–	10–30%	–
Ganglioneuromatosis		–	–	+
Multiple mucosal neuromas		–	–	+
Marfanoid habitus		–	–	+
Thickened corneal fibers		–	–	+

[a] Based on several reports with additional germline *RET* mutation [79–81]; however, it appears that the phenotype is more MEN 2B-like than typical MEN 2B
[b] The age at diagnosis has become younger since the identification of *RET*
[c] Since the identification of *RET*, many patients undergo surgery before MTC occurs
– Disease/finding absent or frequency observed not higher that in the general population
+ Disease/finding present in most cases but neither required nor pathognomonic

So far, the classical MEN 2B phenotype has only been found in patients with germline mutations affecting either codon 918 (>95) or codon 883. Thus, apart from MEN 2B, the affected codon does not distinguish MEN 2A from FMTC as initially believed. The onset of symptoms, however, appears to be determined by the type of mutation. Modifying factors, however, have not yet been determined. Polymorphisms of *RET* and its coreceptors and ligands are thought to play a role [55].

MEN 2 Kindred Without RET Mutation

Since >95% of patients with MEN 2 harbor a germline *RET* mutation, being confronted with an MEN 2 kindred without an *RET* mutation has become a rare event. In these cases, biochemical screening has to be performed as in the pre-*RET* era [56].

Screening

RET mutation analysis is recommended for index patients, and, when a mutation is found, first-degree and subsequent relatives. In patients with MEN 2A/FMTC, genetic testing is advocated at the age of 5–6 years. In patients with MEN 2B, genetic testing should start soon after birth. Since many mutations in MEN 2B are de novo and early symptom often missing, diagnosis and subsequent genetic testing is rarely made before the age of 3–4 years.

Since ~25% of patients with MTC have MEN 2 (75% are sporadic), *RET* germline mutation analysis is recommended in any patient with MTC, irrespective of family history, accompanying disease features and age in order to identify index patients. The absence of C-cell hyperplasia does not exclude the presence of an underlying hereditary disease. Of note, the presence of C-cell hyperplasia does not justify the diagnosis of MEN 2.

About 10% of patients with pheochromocytoma have MEN 2, and about 15% have another hereditary syndrome (e.g., von Hippel-Lindau syndrome, pheochromocytoma–paraganglioma syndrome, neurofibromatosis type 1), while about 75% are sporadic. Therefore, as for patients with MTC, an *RET* germline mutation analysis is recommended for any patient with pheochromocytoma [57].

Since only a minority of all patients with hyperparathyroidism have MEN 2A, an *RET* germline mutation analysis is not generally recommended in patients with hyperparathyroidism and no other suspicion for MEN 2A.

Clinical Aspects

MEN 2 [formerly also named multiple endocrine adenomatosis (MEA)] is a rare endocrine condition; its prevalence has been estimated to be about 1/35,000. MEN 2 is characterized by the coexistence of various endocrine disorders involving the thyroid (MTC), the adrenals (pheochromocytoma), and parathyroids (hyperparathyroidism) (Table 43.4). Additionally, abnormalities affecting nonendocrine tissues/organs may be present. The female to male ratio is roughly 1:1.

Almost all patients with MEN 2 develop hyperplasia of the thyroidal C cells (C-cell hyperplasia, CCH) that is considered a precancerous stage before C-cell carcinoma (MTC) occurs. About 70% of patients develop clinically apparent MTC by the age of 70 years [58]. Since metastasized MTC can only rarely (20–30%) be cured, surgery at an early stage is advocated even if no clinical or paraclinical signs are present.

In addition, about 50% of all patients with MEN 2 develop pheochromocytoma. Malignancy has been reported in less than 5% of MEN 2-associated pheochromocytomas [59, 60] and, thus, is of minor clinical importance.

MEN 2A

MEN 2A is also known as Sipple syndrome [61]. MTC as part of MEN 2A may be found at age 5 and younger, a genotype–phenotype correlation exists (see above). Besides MTC and pheochromocytoma, patients with MEN 2A may develop hyperparathyroidism (10–30%) (Table 43.4). In contrast to MEN 1, pHPT most commonly develops after the third decade of life.

MEN 2B

MEN 2B has also been termed MEN 3 and is less commonly known as Wagenmann–Froboese syndrome. Besides MTC and pheochromocytoma, patients with MEN 2B may develop a marfanoid habitus, neuromas of the tongue, ganglioneuromatosis of the intestine, and/or medullated corneal nerve fibers [62]. Of note, none of these lesions or phenotypes is pathognomonic, i.e., they have also been reported without an MTC or MEN 2B-specific *RET* mutation [63–65].

Familial MTC

Occasionally, the term FMTC is used in families that develop MTC only, i.e., none of the family members show signs of pheochromocytoma and/or hyperparathyroidism. *RET* germline mutations are found in the majority (>95%) of these families. Patients with FMTC are on average older than patients with MEN 2A. However, while the percentage of the various mutations differs between patients with FMTC and MEN 2, the mutations themselves in general do not differ between these two groups (Table 43.4). Hence, neither mutation itself justifies exclusion of the family members from being screened for pheochromocytoma and hyperparathyroidism.

Diagnosis and Imaging

Medullary Thyroid Carcinoma

Neck nodules due to either the primary thyroid tumor or cervical lymph node metastases are the most common signs of MTC. C cells produce calcitonin, a very sensitive but less-specific (other conditions that may be accompanied with elevated calcitonin levels are, e.g., nonthyroidal neuroendocrine tumors, renal insufficiency, pregnancy) marker of MTC and its precursor lesion CCH. Specific for CCH/MTC appears to be their response to provocative agents. Pentagastrin (0.5 μg/kg body weight, injected i.v. in 5–15 s) and calcium (2 mg/kg body weight of 10% Ca^{2+}-injected i.v. in 1 min) have both been used successfully. Pentagastrin appears to be the most effective calcitonin secretory discriminator [66], but there happens to be a worldwide shortage of pentagastrin. An increase of more than two to three times the basal calcitonin level is considered pathologic and indicative for CCH and/or MTC [67]. In the case of high serum calcitonin levels, symptoms may arise, e.g., diarrhea, that do not respond well to antidiarrheic drugs.

The value of basal and stimulated calcitonin levels in screening patients is controversial. Theoretically, surgery should be offered and performed before calcitonin levels become pathologic. If basal and stimulated calcitonin levels are within normal range, lymph node involvement appears to be unlikely and, hence, surgical extent concerning lymph node dissection may be limited (either no lymph node dissection at all or central lymph node dissection only) (Figs. 43.1 and 43.2).

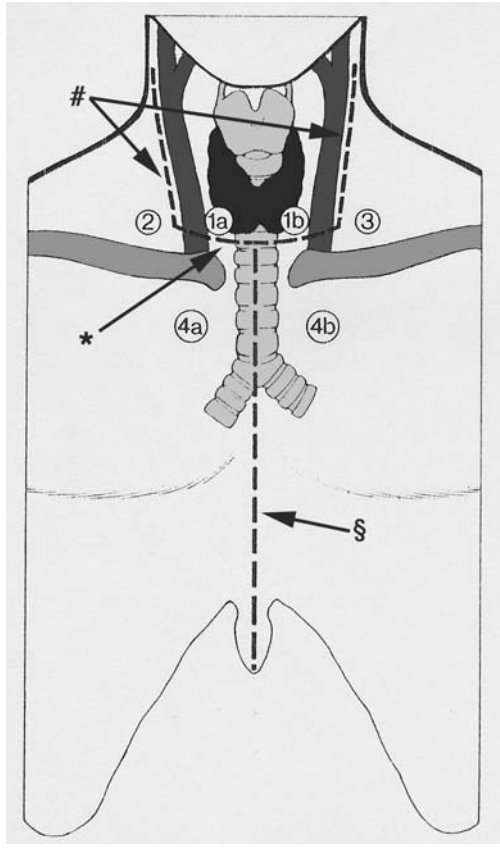

Fig. 43.1. Locoregional compartments. (1a) Right central; (1b) left central; (2) right lateral; (3) left lateral; (4a) right upper mediastinal; (4b) left upper mediastinal; (*) incision for central compartment dissection; (#) extension of incision for lateral compartment dissection; (§) extension of incision for mediastinal dissection.

The latest age to start clinical screening at the latest should depend on the specific *RET* mutation (Fig. 43.2).

Imaging procedures other than ultrasound (CT, MRI, endoscopy) are rarely (e.g., in the case of suspected tracheal and/or esophageal infiltration) indicated prior to primary operation.

Pheochromocytoma

Pheochromocytoma is frequently diagnosed synchronously or metachronously to MTC. In about 10%, pheochromocytoma may precede MTC [59]. In these cases, typical symptoms are hypertension, headache, tachycardia, and sweating.

Pheochromocytoma is diagnosed by finding elevated levels of free catecholamines (epinephrine,

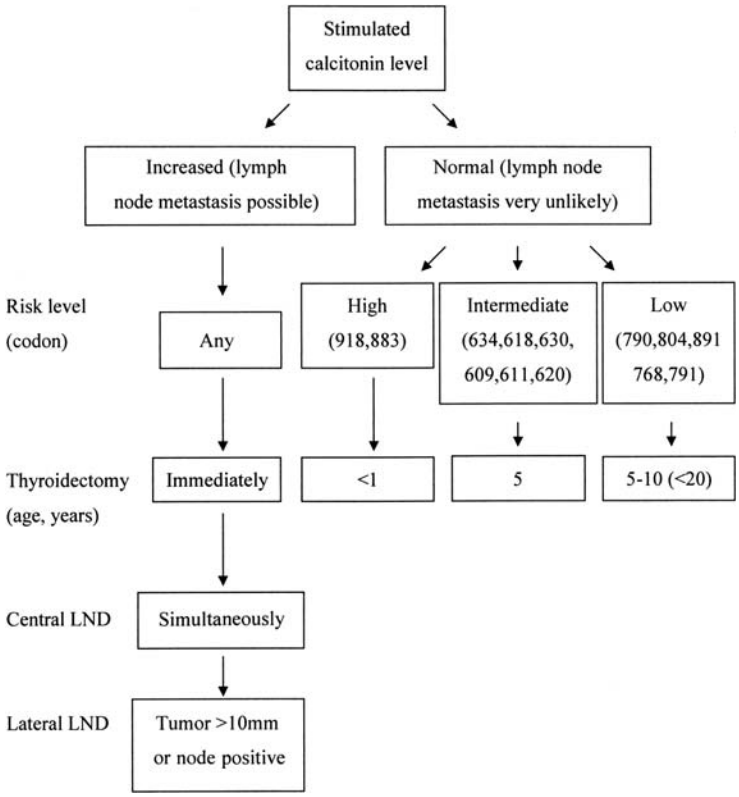

Fig. 43.2. Recommendations for timing and surgical extent in patients with MEN 2/FMTC according to stimulated calcitonin levels, codon mutation, and age. LND: central lymph node dissection.

norepinephrine) or their metabolites (e.g., vanillylmandelic acid, metanephrines) in a 24-h urine collection. Measurement of plasma metanephrines is the most specific test [68].

Biochemical screening for pheochromocytoma should at the latest be started by the age of 10 and either include free plasma metanephrines, plasma or urine catecholamines, or urine vanillylmandelic acid. Imaging studies (ultrasound, CT) are generally performed once the biochemical diagnosis has been made. Patients with clinically suspected FMTC (familial MTC only) should also be screened for the presence of pheochromocytoma since no mutation alone appears to justify the diagnosis FMTC (see above).

Enlarged glands are almost always present if the patient is symptomatic. Both CT and magnetic resonance tomography are excellent (sensitivity almost 100%, specificity 70%) imaging techniques in determining the adrenal localization of the pheochromocytoma. Extraadrenal pheochromocytomas or metastases may better be diagnosed using 131-I-metaiodobenzylguanidine (MIBG) (sensitivity 80%, specificity nearly 100%) or 18-F-DOPA-PET [69], however, pheochromocytomas as part of MEN 2 are rarely extraadrenal or malignant.

Hyperparathyroidism

Hyperparathyroidism is not part of MEN 2B and, by definition, is only seen in patients with MEN 2A and not in patients with FMTC (Table 43.4). The typical symptoms are rarely seen in patients with MEN 2A. However, prior to surgery due to MTC, the possible coexistence of hyperparathyroidism should be assessed, should be treated synchronously when present. Screening for pHPT in MEN 2A patients should include annual measurement of ionized calcium and intact parathyroid hormone. Patients with clinically suspected FMTC (familial

MTC only) should also be screened for the presence of pHPT since no mutation alone appears to justify the diagnosis FMTC (see above). Patients with MEN 2B, however, do not need to be screened for pHPT.

Preoperative imaging techniques are not necessary prior to primary surgery.

Therapy and Prognosis

Medullary Thyroid Carcinoma

Prior to surgery on the thyroid gland, the presence of pheochromocytoma must be excluded. If present, pheochromocytoma must be treated first (see below). Since every C-cell inherits the potency to become malignant, MTC as part of a familial condition is typically bilateral and multifocal. Thus, total thyroidectomy is generally advised in patients with hereditary MTC.

Many lymph node metastases in MTC can neither be detected preoperatively by imaging techniques nor intraoperatively. On the one hand, this fact demands a systematic approach, i.e., lymph nodes and surrounding adipose tissue are removed en bloc while preserving nerves, muscles, and vessels. "Berry picking" should not be performed in patients with MTC. However, the overall extent of lymph node dissection is difficult to determine. Hereditary MTC is often multifocal, and hence, patients have an increased risk of developing lymph node metastases [70]. In general, index patients (i.e., patients with clinical symptoms of MTC) require central and bilateral lateral lymph node dissection (Fig. 43.1). In contrast, the extent of lymph node surgery in screen-detected patients may vary from none to central only to central plus bilateral lateral lymph node dissection (Fig. 43.1). The level of calcitonin may be helpful in determining the surgical extent. Patients with normal calcitonin levels both basal and after stimulation with pentagastrin are very unlikely to have lymph node metastases. In this regard causes the worldwide shortage of pentagastrin a dilemma for patients with MTC. If calcitonin is elevated, the likelihood of MTC and lymph node metastases increases. A calcitonin-dependent, codon-specific, and age-related recommendation concerning the extent of surgery is given in Figure 43.1. In the copresence of pHPT, surgery should be carried out as described below.

The prognosis of patients with hereditary MTC is often considered to be better than that of patients with sporadic MTC. This may be, at least in part, due to the younger age at diagnosis because of surveillance and therefore time bias. MTC as part of MEN 2B is often considered to be the most aggressive form of MTC, patients aged 6 months and younger may have developed MTC. However, when adjusted to age, the difference is less obvious [71, 72]. Patients without lymph node metastases at the time of primary operation have an excellent prognosis [73].

Pheochromocytoma

Due to the genetic background, both glands may be involved, either synchronously or metachronously. Subtotal resection may therefore be considered at primary surgery.

Since MEN 2-associated pheochromocytoma is almost always benign, the prognosis of patients is mainly determined by the clinical course of their MTC. However, the presence of pheochromocytoma needs to be excluded prior to surgery of MTC, and, if present, should be treated first.

Hyperparathyroidism

In contrast to MEN 1, hyperparathyroidism as part of MEN 2 is often mild and requires generally neither subtotal parathyroidectomy nor total parathyroidectomy and autotransplantation. However, all parathyroid glands should be visualized intraoperatively. Enlarged glands should be removed. In the rare event that all glands are enlarged, the same approach as in MEN 1 may be followed. The prognosis of MEN 2-associated hyperparathyroidism is generally excellent. However, a few cases with severe forms have been described.

Follow-Up

As for patients with MEN 1, follow-up should be lifelong.

Medullary Thyroid Carcinoma

Following surgery for MTC, basal and stimulated calcitonin levels should be measured at least biannually during the first 5 years and then annually. In the case of increasing levels,

imaging techniques (CT, MRI, octreotide scintigraphy [74], and FDG-PET [75]) may be performed to localize the tumor burden. Calcitonin and carcino-embryonic antigen (CEA) doubling times appear to be good predictors of survival [76]. Of note, falling levels of calcitonin are not always associated with decreasing tumor burden but may indicate tumor dedifferentiation [77]. In these cases, CEA may be a better predictor of outcome. All patients require lifelong substitution of thyroid hormone replacement; thyroid-stimulating hormone suppression as in differentiated thyroid carcinoma is not necessary.

Pheochromocytoma

Contralateral tumor development or, in the case of subtotal adrenalectomy, ipsilateral tumor recurrence can occur, and lifelong follow-up is mandatory. If bilateral total adrenalectomy has been performed, the patient requires glucocorticoid and mineralocorticoid replacement and close postoperative monitoring [78].

Hyperparathyroidism

Recurrent/persistent disease after surgery is rare. If present, the same guidelines as for MEN 1 apply.

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Section VI
Carcinoid

44

Carcinoid: Presentation and Diagnosis, Surgical Management

Göran Åkerström, Per Hellman, and Peter Stålberg

Introduction

The name "carcinoid" was first used by Oberndorfer in 1907 to describe uncommon ileal tumors with benign behavior in contrast to common bowel carcinomas. The term was subsequently used as an overall name for neuroendocrine cell-derived tumors. Based on their embryological origin these tumors have commonly been classified into foregut, midgut, and hindgut carcinoids. In recent classifications the carcinoids have been named neuroendocrine tumors of the respective organs, and classified into the categories: well-differentiated neuroendocrine tumors, well-differentiated endocrine carcinoma, poorly differentiated endocrine carcinomas, and mixed exocrine–endocrine tumors [1]. In this chapter we will cover the clinical presentation, diagnosis and surgical management of carcinoids, and for clarity have used a common older classification. Carcinoids are rare with an incidence of 1–2/100,000 population/year. About 70% occur in the gastrointestinal tract [2]. They typically stain positively for chromogranin A and/or synaptophysin. The majority are differentiated (with low mitotic activity and low Ki67 proliferation index, often $<2\%$), while others are intermediate or poorly differentiated, with an increased mitotic rate and higher proliferation (Ki67 index 10–40%) [1]. Most carcinoids are clinically nonfunctional, but some have dominant secretion (serotonin, histamine, gastrin, somatostatin), sometimes causing severe symptoms. The most common is the carcinoid syndrome, associated with the "classical" midgut jejuno-ileal carcinoid. Rare foregut carcinoids can have ectopic adrenocorticotropic hormone (ACTH) or corticotropin-releasing factor (CRF) secretion, causing ectopic Cushing's syndrome [1]. The well-differentiated tumors often have an extended clinical course and therefore have specific surgical requirements based on tumor type and localization.

Gastric Carcinoids

Gastric carcinoids are rare, although the incidence is rising due to an increased awareness and use of endoscopic investigations. They currently constitute ~8% of all carcinoids and 1% of gastric neoplasms [2]. Incidence is high in Japan, possibly due to prevalent chronic atrophic gastritis [3].

Most carcinoids derive from enterochromaffin-like (ECL) cells in the body or fundus of the stomach. Three distinct types are recognized:

Type 1 Gastric Carcinoids

Type 1 ECL gastric carcinoids represent ~75% of gastric carcinoids and occur secondary to

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hypergastrinemia in <1% of patients with autoimmune chronic atrophic gastritis (ACAG) (Fig. 44.1) [1–5]. They are most frequent in older females, with a mean age of ~65 years. Vitamin B_{12} malabsorption is common, and ~50% of patients have pernicious anemia.

ACAG is caused by antibodies to parietal cells leading to chronic atrophic gastritis, with gastrin cell hyperplasia and hypergastrinemia due to the absence of acid blockade. Mucosal atrophy of the body and fundus occurs, and ECL-cell hyperplasia or dysplasia is invariably present. Type 1 carcinoids are typically small (<1 cm), multiple polyps (>50%) with obvious surrounding mucosal atrophy (Fig. 44.2). The number of polyps is variable, while some appear solitary and may be difficult to distinguish from adenomatous polyps, which also occur in ACAG. They rarely ulcerate or bleed. Most lesions are benign, and are limited to the

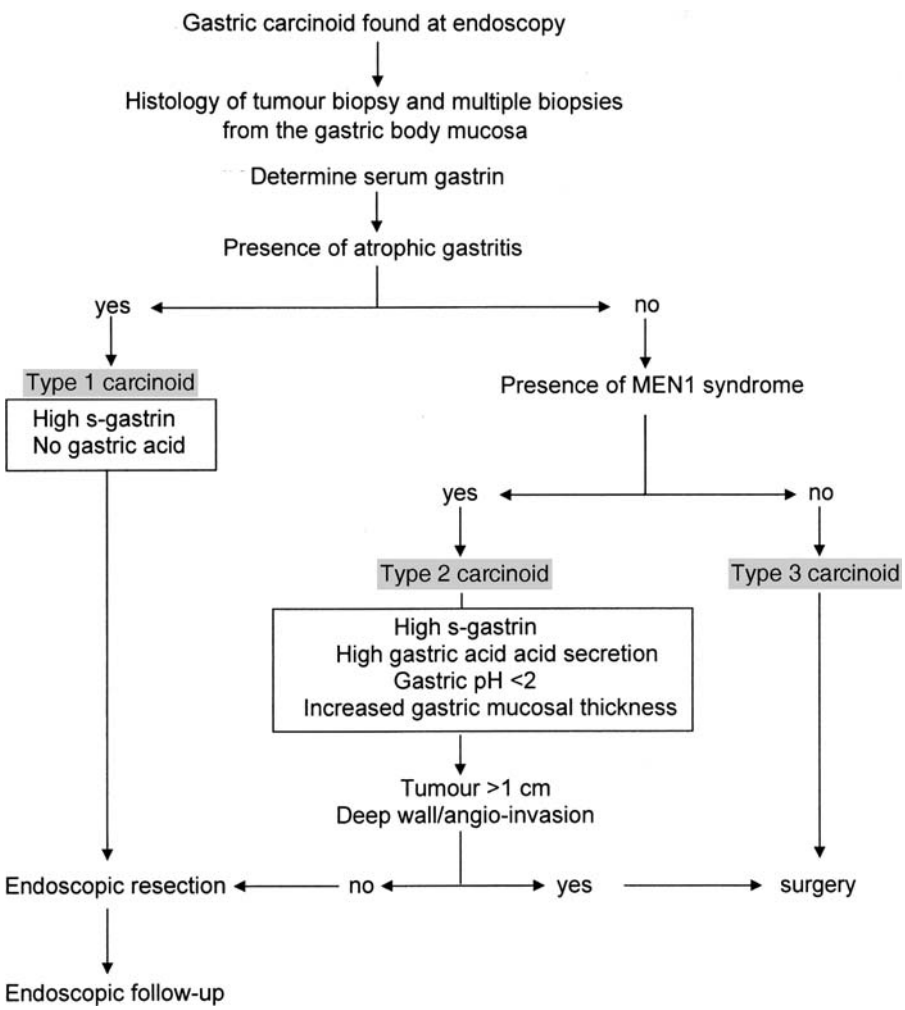

Fig. 44.1. Management of patients with gastric carcinoid found at endoscopy. Demonstration of atrophic gastritis in the gastric body mucosa is a key point, allowing classification as type 1 gastric carcinoid. If atrophic gastritis is not found, the patient should undergo screening for MEN1 and ZES (type 2 gastric carcinoid). If neither chronic atrophic gastritis nor MEN1 is diagnosed, the patient has the more aggressive type 3, sporadic gastric carcinoid. This figure was redrawn with permission from Best Practice and Research in Clinical Gastroenterology, vol. 19, Delle Fave G, Capurso G, Milione M, Panzuto F, Endocrine tumors of the stomach, 659–73, copyright Elsevier 2005; and from Åkerström G, Hellman P, Surgery on neuroendocrine tumors, in: Öberg K, Eriksson B, editors, Best Practice and Research: Clinical Endocrinology and Metabolism, vol. 21, pp. 87–110, copyright Elsevier 2007.

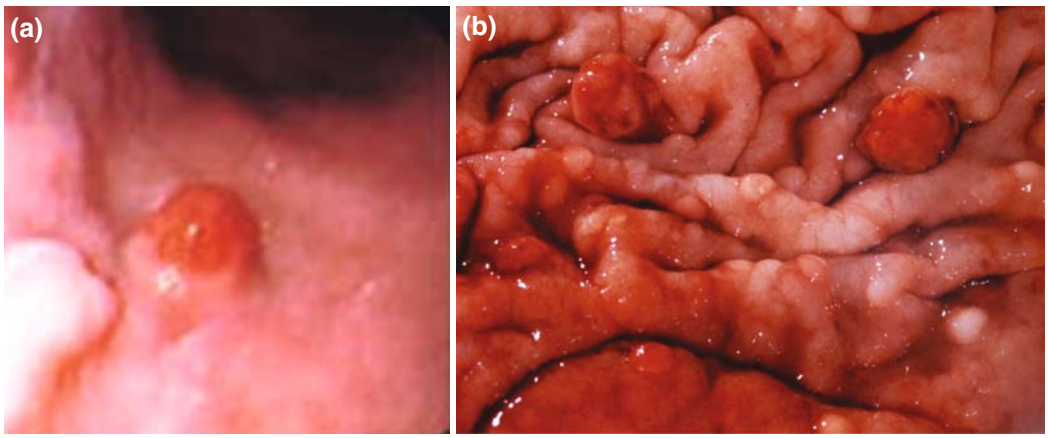

Fig. 44.2. ECL-cell gastric carcinoids type 1 **(a)** and type 2 **(b)**. Reprinted from WHO Classification of Tumors. Pathology & Genetics – Tumors of Endocrine Organs (2004, p. 220), with permission.

submucosa, with the muscularis layer involved in a minority of cases (7%). The tumors are typically argyrophilic with silver stains, and show intense chromogranin A immunoreactivity and an absence of serotonin reactivity. Vesicular monoamine transporter type 2 (VMAT-2) staining is positive, and the proliferation index is typically low.

Type 1 carcinoids rarely cause symptoms and are usually an incidental finding at endoscopy, or found during screening of ACAG patients. Lymph node metastases occur in 5%, liver metastases in 2.5%, disease-related deaths are exceptional or not reported.

Diagnosis. Serum gastrin and chromogranin A values are invariably raised. Antiparietal cell and antiintrinsic factor autoantibodies are present in ~50% of patients. Gastric aspiration for the determination of gastrin acid output is often not necessary, but confirms achlorhydria in difficult cases (Fig. 44.1) [5].

Surgical treatment. Small carcinoids <1 cm associated with ACAG have a minimal risk for invasion and should undergo surveillance. Endoscopic mucosal resection is recommended for lesions close to and above 1 cm without invasion of the muscularis propria [5, 6]. This is also recommended for multiple (up to 6) polyps without invasion. Surgical excision is recommended for larger tumors invading the muscularis propria, preferably evaluated by endoscopic ultrasound (EUS). Exceptional cases with large, multifocal, or recurrent lesions or those with regional metastases may require gastric resection with lymph node dissection. Antrectomy may cause regression of type 1 carcinoid polyps, but is not invariably recommended, because clinically significant lesions generally remain unaffected [7]. Follow-up with yearly endoscopic surveillance and multiple gastric biopsies is needed. Treatment with somatostatin analogues may help prevent recurrence.

Type 2 Gastric Carcinoids

ECL cell hyperplasia is seen in 80% of patients with multiple endocrine neoplasia type 1 (MEN1) and the Zollinger–Ellison syndrome (ZES). About 5–30% of the patients develop carcinoids in the gastric body and fundus and occasionally in the antrum [1, 3–5]. Type 2 carcinoids represent 6% of gastric endocrine tumors without gender predilection, and occur at a mean age of ~50 years. Patients have a hypertrophic, hypersecretory gastropathy, with high levels of circulating gastrin, and increased gastric acid secretion. ECL cell hyperplasia and dysplasia can be seen in the nontumoral mucosa of the fundus, which has an increased thickness, in contrast to the atrophy of type 1 lesions. Patients with sporadic ZES may often also have ECL cell hyperplasia, but rarely (<1%) gastric carcinoids. The type 2 carcinoids are usually multiple and <1.5 cm in size, and may occupy

the entire fundic mucosa (Fig. 44.2). Occasionally tumors are larger (>4 cm). Lymph node metastases occur in ~30% of patients and liver metastases in 10–20% [1, 3–5, 8]. The malignant potential of these lesions is intermediate between ACAG-associated and sporadic gastric carcinoids. The type 2 carcinoids are generally asymptomatic although some tumors demonstrate local invasion, angioinvasion, and a higher proliferation rate. Aggressive tumors with liver metastases are more frequent with long-standing ZES, and poorly differentiated gastric endocrine carcinomas have occasionally been encountered. They are the cause of death in ~10% of patients.

Diagnosis. Patients often have other features of MEN1, noted previously or at the time of diagnosis. Patients have a raised serum gastrin, together with hypertrophic gastric mucosa and high gastric acid secretion (gastric pH <2) (see below) (Fig. 44.1).

Surgical treatment. Surgery is focused on removing the source of the hypergastrinemia. It is important to consider excision of duodenal gastrinomas, typical of MEN1 patients, via a duodenotomy, combined with clearance of lymph node metastases (see below) [9–11]. For type 2 carcinoids only local excision is recommended. Gastric resection together with regional lymph gland clearance is performed for larger tumors, or those with deep wall invasion or angioinvasion. If hypergastrinemia is not reversed by surgery then somatostatin analogue treatment may reduce tumor growth, especially in the presence of multiple tumors [4].

Type 3 (Sporadic) Gastric Carcinoids

Type 3 ECL carcinoids are not associated with hypergastrinemia or ACAG. They occur in nonatrophic gastric mucosa without endocrine cell proliferation (Fig. 44.3) in patients with normal gastrin. They account for ~15% of gastric carcinoids and occur most frequently in males, with a mean age of ~55 years. Determination of serum calcium and family history will help exclude MEN1 (Fig. 44.1) [1, 3–5]. These carcinoids are usually solitary and large, often >2 cm (33%). Rare multiple tumors have been observed. Some tumors occur in the antral or prepyloric region, although the majority are located in the gastric body and fundus. Invasion of the muscularis is seen in ~75% and serosa in 43% of cases.

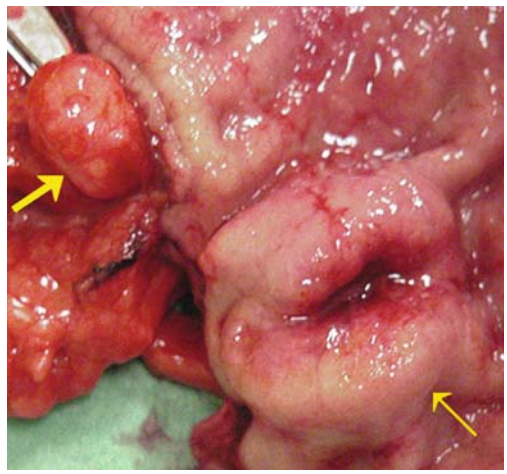

Fig. 44.3. Sporadic gastric carcinoid type 3 (*thin arrow*) with lymph gland metastasis (*thick arrow*).

Type 3 tumors present as a mass lesion, typically without endocrine symptoms, with clinical findings similar to adenocarcinoma, including gastric hemorrhage, iron-deficiency anaemia, gastric obstruction, and metastases. An "atypical carcinoid syndrome" occurs in 5–10% [1]. The syndrome is due to release of histamine and is characterized by a patchy geographic, intense red flush, cutaneous oedema, bronchospasm, salivary gland swelling and lacrimation, but absence of diarrhea. It is usually coupled with the presence of liver metastases and production of histamine and 5-hydroxytryptophan. Urinary estimates of the histamine metabolite methylimidazole-acetic acid (MelmAA) serves as a tumor marker, and patients may have slight elevation of urinary 5-hydroxy-indoleacetic acid (5-HIAA) values.

Regional lymph node metastases occur in 71% and distant metastases in 69% of patients [1, 3–5, 12]. Ki67 index is generally >2%. Most tumors originate in ECL cells, but other cell types may be present and associated with a less favorable prognosis. Sporadic carcinoids can have an atypical histology, with pleomorphism, high mitosis rate, and higher Ki67 index (10–15%). The atypical tumors are larger, mean ~5 cm, more frequently invasive, and have an unfavorable survival [1, 13].

Diagnosis is based on the demonstration of a generally solitary, larger gastric carcinoid, in patients without hypergastrinemia and in the absence of mucosal atrophy or ECL-cell hyperplasia. The presence of metastases should be assessed preoperatively with Octreoscan and CT (Fig. 44.1).

Surgical treatment. The sporadic gastric carcinoids are treated with gastric resection combined with regional lymph node clearance. Tumors >2 cm or those with atypical histology or gastric wall invasion are most appropriately dealt with by gastrectomy. The overall 5-year survival is ~50%, and ~10% in patients with distant metastases.

Non-ECL-Cell Gastric Carcinoids

Uncommon gastrin cell-derived tumors occurring in the prepyloric region, may cause ZES secondary to gastrin production. Rare tumors may present with ectopic Cushing's syndrome due to ACTH secretion.

Poorly Differentiated Gastric Carcinoids

Poorly differentiated gastric carcinoids are identical to small cell carcinomas of the lung, and occur mainly in elderly patients as highly malignant, aggressive tumors with extensive local invasion and spread metastases at diagnosis [1]. Half of the patients have atrophic gastritis. The tumors may be ulcerated or fungating, with a size of ~4–5 cm, and high proliferation index of 20–40%. Prognosis is poor with median survival of 8 months; few individuals have longer survival [3–5]. Generally the tumors are not resectable, although surgical debulking and chemotherapy may occasionally be considered in patients with mixtures of well- and poorly differentiated tumors.

Duodenal Carcinoids

Carcinoids of the duodenum are rare in older series, comprising ~2–3% of gastrointestinal endocrine tumors, but have a rising incidence due to increased diagnosis [1, 14, 15].

Gastrinoma

Gastrin-cell (G-cell) tumors, gastrinomas, represent the largest group (~60%) of duodenal endocrine tumors, 15–30% of G-cell tumors cause clinical ZES, while the remainder are clinically silent [1, 14]. Since 1989 duodenal gastrinomas have been recognized as the most common gastrinomas, causing ~60% of sporadic ZES, and ~90% of MEN1-associated ZES [16, 17]. The duodenal gastrinomas responsible for ZES occur within the duodenal submucosa, most often in the first and second part of the duodenum [1, 16, 17]. Duodenal gastrinomas are frequently small (≤0.5 cm), with early regional lymph nodes metastases reported in 30–70% of patients (Fig. 44.4) [1, 16, 17]. The lymph node metastases are often larger than the primary tumors, which may be difficult to detect at operation. Liver metastases tend to develop late, and affect ~10% of patients, providing possibilities for curative treatment [18, 19]. The smallest duodenal gastrinomas may present as

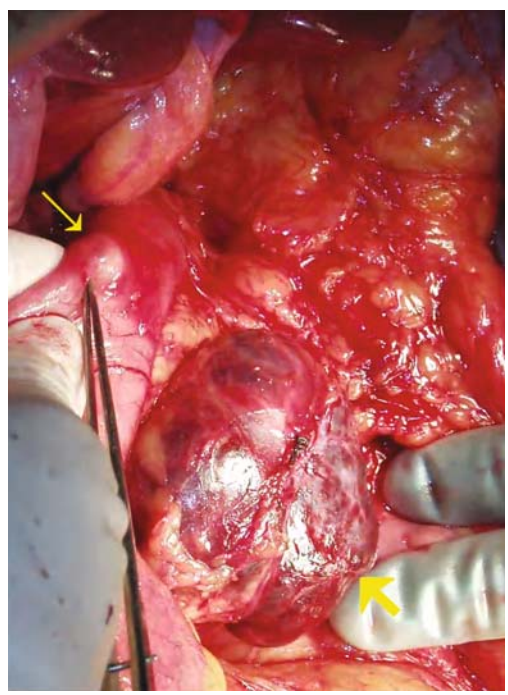

Fig. 44.4. Small duodenal gastrinoma (*thin arrow*) in proximal duodenum, and 5 cm large lymph gland metastasis in front of the pancreas (*thick arrow*).

"primary lymph node gastrinoma," which is diagnosed in up to 10% of patients with ZES, where the primary tumor remains undetected. While the majority of gastrinomas are sporadic, up to 30% occur as part of the MEN1 syndrome. MEN1/ZES patients typically have multifocal gastrinomas [20–22].

Diagnosis. ZES is a rare cause of peptic ulcer disease with recurrent, atypically located, multiple and complicated ulcers, and/or esophagitis, sometimes concomitant diarrhoea, and in 20% solely diarrhoea [1, 22]. Gastrin levels tend to be markedly raised, together with high basal gastric acid output and low gastric pH. Serum gastrin >1,000 pg/ml and gastric pH <2 is diagnostic of ZES. If this criterion is not fulfilled a secretin test may be required, and is diagnostic with paradoxal rise in gastrin (≥200 pg/ml over baseline), but 15% of ZES patients have a negative test. The crucial differential diagnosis is atrophic gastritis, where patients have high gastrin without gastric acid (gastric pH >3 excludes ZES).

Preoperative localization. CT or MRI is routinely undertaken in ZES patients to visualize lymph node and liver metastases prior to surgery [23]. Octreoscan reveals lymph node and liver metastases in ~90%, and occasional larger primary tumors, but rarely detects small duodenal tumors. Large lymph node metastases around the pancreatic head are easily mistaken to represent the primary tumor. Duodenal gastrinomas in ZES are rarely identified by endoscopy because of their small size. EUS can detect some larger duodenal gastrinomas, and often lymph node metastases, but rarely the smallest duodenal tumors. The selective arterial stimulation test (SAS, Imamura test), with injection of pentagastrin may provide tumor regionalization, and demonstrate liver metastases [24]. In the absence of positive localization, patients with ZES should be liberally submitted to surgery, because these patients are likely to harbor resectable duodenal gastrinomas [22, 23].

Surgical treatment. The surgical cure rate in ZES patients has risen markedly since it has been appreciated that a majority of gastrinomas occur in the duodenum [25]. Endoscopic transillumination has been advocated, but duodenal gastrinomas are most efficiently visualized during surgery via a longitudinal duodenotomy after inversion of the lumen with careful inspection and palpation of the entire duodenum. The smallest duodenal submucosal tumors can be removed by mucosal dissection, tumors larger than 5 mm require duodenal wall excision. Pancreaticoduodenectomy may be required for the occasional larger duodenal tumors (and for pancreatic head gastrinomas). Surgery in patients with gastrinoma should include a thorough clearance of peripancreatic lymph node metastases, and also aim to remove resectable liver metastases [25, 26].

Gastrinomas should always be considered potentially malignant. However, duodenal gastrinomas have been considered a potentially curable entity of ZES. The duodenal gastrinomas in ZES are (in contrast to pancreatic gastrinomas) slow-growing, indolent malignancies despite their tendency to spread to local lymph nodes. Survival is thus favorable in patients with duodenal gastrinomas and lymph node metastases, removal of which possibly limits further spread, and few (~10%) of these patients develop liver metastases [25, 26].

Overall adverse prognostic factors for gastrinomas are large primary pancreatic tumors, presence of liver or bone metastases, and very high serum gastrin. The small duodenal gastrinomas have a markedly slow progression with ~90% 10-year survival (in contrast to pancreatic gastrinomas with ~60% 10-year survival). Recurrence is almost inevitable in patients with multiple gastrinomas associated with MEN1 ZES subjected to anything short of a pancreaticoduodenectomy. This is often not considered to be indicated, because of the risk of concomitant or subsequent pancreatic body and tail tumors in these patients.

Somatostatin-Rich Carcinoids

Carcinoids with somatostatin immunoreactivity comprise 15–20% of duodenal endocrine tumors, although the majority of these are clinically nonfunctioning [1, 15, 22]. They almost exclusively occur at the ampulla of Vateri, as a 1- to 2-cm homogeneous nodule, that is occasionally polypoid, ulcerated, or larger in size. Clinically they cause obstructive jaundice, pancreatitis, or bleeding. Regional lymph node or liver metastases occur in ~50% of patients. These tumors have a glandular growth pattern, contain specific laminated psammoma bodies, and stain with chromogranin A. One third are associated with von

Recklinghausen's neurofibromatosis type 1 (NF1), and occasionally with pheochromocytoma [27]. Dependent on tumor size and patient age, the somatostatin-rich carcinoids may be locally excised or require pancreaticoduodenectomy.

Gangliocytic Paraganglioma

These are rare tumors, occurring almost exclusively in the second portion of the duodenum, sometimes associated with NF1 [1]. The tumors consist of a mixture of paraganglioma, ganglioneuroma, and carcinoid tissue with reactivity for somatostatin and PP. They are generally benign and recognized incidentally at gastroscopy or because of bleeding. They have had excellent prognosis after surgical excision.

Other Duodenal Carcinoids

Unusual, well-differentiated duodenal carcinoids may be reactive for other hormones such as calcitonin, pancreatic polypeptide (PP), and serotonin [1]. Most of these tumors are found as small polyps (<2 cm) in the proximal duodenum. Multiple tumors should raise suspicion of an associated MEN1 syndrome. The majority are low-grade malignant tumors often suitable for local surgical excision, and only rare, large tumors require pancreaticoduodenectomy.

Another group of duodenal carcinoids without hormone reactivity or secretion, but with positive chromogranin A, synaptophysin and/or NSE reactivity, may be recognized. Many are asymptomatic and incidentally found at endoscopy, while others present with abdominal symptoms, gastrointestinal bleeding, and sometimes vomiting or weight loss [1]. Most of these tumors are located in the first portion of the duodenum, occasionally in the second part and rarely in the third portion (horizontal duodenum). Up to one third of the patients have previously had other primary malignancies; including adenocarcinoma of the gastrointestinal tract, prostate, or other organs [1].

More than half of these tumors are smaller than 2 cm, and generally have a good prognosis and rarely metastasize. Size >2 cm, invasion beyond the submucosa, or presence of mitotic figures are independent risk factors for metastases, or recurrence after surgery [1, 15].

Surgical treatment. Lesions <1 cm can be endoscopically excised, but follow-up endoscopy is required to ensure complete removal [1]. Tumors <2 cm, without evidence of invasion of the muscularis, can be treated with local excision. Larger tumors require segmental duodenal resection or pancreaticoduodenectomy to reduce the risk of recurrence [1, 5]. Periampullary tumors have a more malignant behavior and require radical surgery. Patients with metastasizing duodenal carcinoids may survive for decades, substantiating that they are often less aggressive than adenocarcinomas.

Poorly Differentiated Duodenal Carcinoids

Poorly differentiated neuroendocrine carcinomas in the duodenum are exceptionally rare. Most occur at the ampulla of Vateri. Patients typically present with obstructive jaundice, and have a rapidly fatal course [1, 14].

Midgut Carcinoids

The midgut, ileo-jejunal carcinoids account for ~25% of gastrointestinal carcinoids, and have been increasingly diagnosed due to raised awareness [1, 2, 22, 28]. The tumors are equally prevalent in males and females, occurring from the third decade with a peak around ~65 years of age. They originate in EC cells, usually in the terminal ileum, and less commonly (≤10%) in the jejunum. The primary tumor is typically submucosal and small, ~1 cm in diameter, flat and seldom ulcerated, and therefore rarely bleeds [1, 2, 22, 28]. Occasional larger tumors, or those accompanied with fibrosis of the intestinal serosa, may cause intestinal obstruction (Fig. 44.5). In 25–30% of patients multiple, smaller tumors can be seen in proximity, probably due to submucosal lymphatic spread. Rarely patients also have multiple carcinoid polyps in the proximal part of the intestine, possibly representing real multifocal origin. Mesenteric lymph node metastases are common even with small primary tumors, and microscopic metastases can almost invariably be demonstrated if carefully searched for [29, 30]. Mesenteric metastases tend to grow conspicuously large, and can be mistaken for the primary

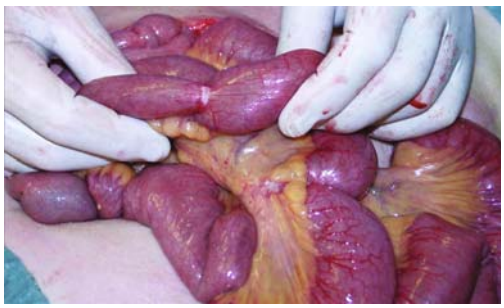

Fig. 44.5. Midgut carcinoid with fibrotic reaction close to obstructing the intestinal lumen.

tumor if located close to the intestine [28]. With more extensive metastatic involvement of the mesentery, serotonin and growth factor release stimulates a desmoplastic, fibrotic reaction, which contracts the mesentery and may angulate and kink the intestine, causing intestinal obstruction. A large mesenteric tumor high in the mesenteric root is often attached by fibrosis to the retroperitoneum and the serosa of the horizontal duodenum, which may become occluded causing a high obstruction [1, 28]. The mesenteric vessels will ultimately be involved in the process, with resulting venous stasis and incipient ischemia in segments of the small intestine. Ultimately conglomerates of distal intestinal loops become fixed to the anterior and posterior abdominal wall and sometimes deeper to the retroperitoneum in the right iliac fossa causing hydronephrosis. Repeat operation tends to further increase fibrosis. Liver metastases are present at diagnosis in ~50% of patients, and ultimately develop in a majority of patients. Extraabdominal metastases may occur in the skeleton, lungs, mediastinum, peripheral lymph nodes, ovaries, breast, and skin [1].

Symptoms. Midgut carcinoids are generally indolent tumors with a slow disease course. Some patients experience unspecific abdominal pain and diarrhea for several years before diagnosis [1, 22, 29], while others have unrecognized features of the carcinoid syndrome, such as discrete flushing after the intake of certain food or alcohol. In nearly half, the disease is diagnosed following more frequent attacks of severe abdominal pain, or surgery for intestinal obstruction of uncertain cause. Other patients have more advanced disease with diagnosis made after the detection of liver metastases, which ultimately develop in the majority of patients.

Carcinoid syndrome. Advanced midgut carcinoid is the most common cause of the carcinoid syndrome, occurring in ~20% of patients with liver metastases. Monoamine-oxidase activity of the liver can detoxify substances released from carcinoid tumors, and the presence of the syndrome generally implies that the patient has liver metastases. In ~5% of patients the syndrome develops in the absence of liver metastases but with extensive retroperitoneal lymphatic spread or ovarian metastases, when tumor secretory products exceed the detoxifying capacity, or bypass the liver and drain into the systemic circulation. Patients with the carcinoid syndrome suffer from flushing, diarrhea, right-sided heart valve fibrosis, and occasionally symptoms of bronchial constriction.

Diagnosis. Plasma chromogranin A is a sensitive marker and is used to detect recurrence and monitor disease progress. However a false-positive rise in chromogranin A can occur with renal impairment, atrophic gastritis, inflammatory bowel disease, and certain medications, e.g., proton pump inhibitors. Raised levels of the serotonin metabolite 5-HIAA in 24-h urine samples is specific for carcinoids, but present only in advanced cases, generally with liver metastases. Contrast enhanced CT can efficiently demonstrate mesenteric and liver metastases, retroperitoneal tumor extension, and reveal the relation to the mesenteric artery and vein. Somatostatin receptor scintigraphy is positive in ~80% and can determine spread to the liver and extraabdominal sites. Recently positron emission tomography (PET) with ^{11}C-5-hydroxytryptophan (HTP) or ^{18}F-dihydroxyphenylalanine (DOPA) has demonstrated superior sensitivity in the detection of minimal tumor deposits of endocrine tumors. PET with ^{18}F-deoxyglucose (FDG) is rarely positive in low-proliferative carcinoid tumors. Ultrasound is routinely used to guide the needle biopsy of lymph node and liver metastases, with staining for chromogranin A and synaptophysin to diagnose carcinoids, and serotonin immunoreactivity to verify the origin as the midgut.

Early surgical treatment. When patients with midgut carcinoids are subjected to emergency surgery with an unknown diagnosis, the tumor

entity can be recognized by the characteristic features of a tiny ileal tumor and larger mesenteric metastases with surrounding fibrosis [1, 22, 28–30]. The tumor should be removed with wedge resection of the mesentery and careful dissection of lymph node metastases around the mesenteric artery and vein, aiming to preserve the vascular supply and limit the intestinal resection. Intestinal bypass is avoided as far as possible because ischemia may develop in the involved intestinal segment and long survival is expected. Mesenteric tumor removal is indicated even in presence of liver metastases, and if not efficiently done at the initial surgery, reoperation is recommended to prevent future abdominal complications. With radical tumor removal patients may remain symptom-free for long time periods. However, carcinoid tumors are tenacious and recurrence with liver metastases will occur in ~85% of patients if follow-up is long enough [1, 22, 28, 31]. Earlier diagnosis of recurrence may be obtained with measurement of chromogranin A.

Surgery for advanced carcinoids. Treatment with long-acting somatostatin analogues can provide efficient control of the carcinoid syndrome and improve quality of life for patients. However, continuous growth of the mesenteric tumors and fibrosis threatens to cause further vascular and intestinal entrapment, resulting in obstruction and compromised intestinal circulation. In many patients this will result in abdominal pain, weight loss, and diarrhea, and some patients will even become cachectic due to incipient ischemia and malabsorption [1, 22, 28–31]. Since the entrapment may contribute significantly to diarrhea, early surgical removal of mesenteric metastases is recommended also as prophylaxis in asymptomatic patients. Further progression and delayed surgery may render the metastases unresectable [32].

With carcinoids originating in the terminal ileum, the mesenteric tumor tends to be deposited to the right side of the mesenteric artery. A special technique for mesenteric root dissection can allow the mesenteric metastases to be more safely dissected from the mesenteric artery and vein, with preservation of the mesenteric circulation (Fig. 44.6). This may limit the intestinal resection and avoid creating a short bowel syndrome. Generally, part of the right colon is removed together with the terminal ileum because of its commonly impaired vascular supply.

Preoperative imaging. Mapping of tumor extension in the mesenteric root with dynamic CT is essential when the dissection of mesenteric metastases is undertaken. Large mesenteric tumor and metastases associated with high ileal or jejunal carcinoids may completely surround the mesenteric root or extend above the pancreas in the retroperitoneum. These

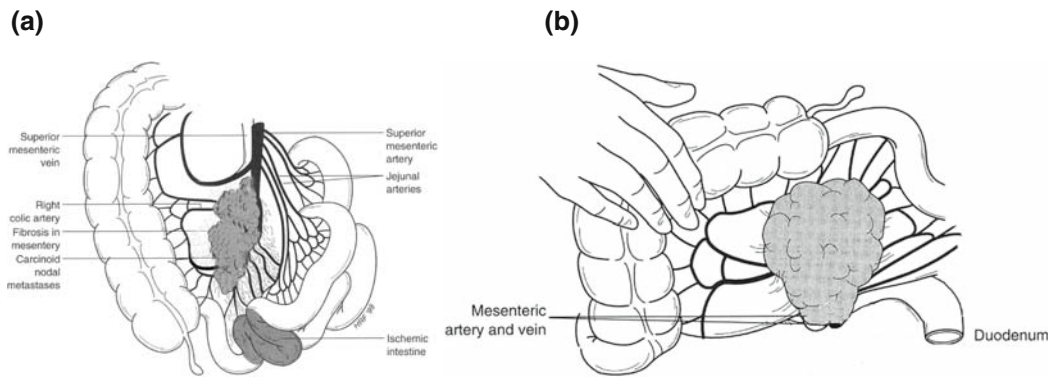

Fig. 44.6. Resection of midgut carcinoid primary tumor and mesenteric metastasis. **(a)** Mesenteric tumor may extensively involve the mesenteric root. **(b)** Mobilization of cecum, terminal ileum, and mesenteric root allows the tumor to be lifted, approached also from posterior angle, and separated from duodenum, pancreas, and main mesenteric vessels with preservation of intestinal vascular supply and intestinal length. Reprinted with permission from Åkerström G, Hellman P, Surgery on neuroendocrine tumors, in: Öberg K, Eriksson B, editors, Best Practice and Research: Clinical Endocrinology and Metabolism, vol. 21, pp. 87–110, copyright Elsevier 2007; and from Åkerström G, Hellman P, Hessman O, Gastrointestinal carcinoids, in: Lennard TWJ, editor, Endocrine Surgery, 3rd ed., pp. 163–98, copyright Elsevier 2006.

tumors may be inoperable or suitable for debulking only.

Results of surgery and prognosis. Removal of mesenteric metastases can relieve abdominal symptoms, reduce the risk for abdominal complications, and may also increase survival [31, 33]. The survival of patients with midgut carcinoids has markedly improved with combined medical and surgical treatment, but strongly depends on the extent of disease. The presence of liver metastases and carcinoid heart disease are the most significant adverse prognostic factors for survival. The 5-year survival has been ~40% with inoperable liver and mesenteric metastases [31, 33].

Prophylaxis against carcinoid crisis. Surgery in patients with the carcinoid syndrome may cause a carcinoid crisis with excessive flush, shock, arrhythmia, bronchial obstruction, or hyperthermia. Routine preoperative prophylactic treatment with intravenous somatostatin analogue (Octreotide, 500 μg in 500 ml saline, 50 μg/h) is recommended [1, 22, 28].

Appendiceal Carcinoids

Appendiceal carcinoids were the most common intestinal carcinoids but have decreased in incidence, and currently represent ~8% of carcinoids, but still account for 50–75% of all appendix tumors [1–3, 22]. The age of presentation is generally younger than for other carcinoids, mean ~40 years, with a female predominance, and children may also be affected.

Diagnosis. The tumor is most common at the tip of appendix, which rarely obstruct the lumen and cause appendicitis. Less than 10% are located in the appendix base. The tumor is found in 1 in 300 appendectomies, but is frequently an incidental finding in appendectomy specimens. The presence of the carcinoid syndrome is exceedingly rare and seen only in patients with massive liver or retroperitoneal metastases.

Surgical treatment. Approximately 90% of appendiceal carcinoids are smaller than 1 cm, not situated in the appendix base, and are cured by appendectomy [22, 34, 35]. Tumors >2 cm should be treated with hemicolectomy and ileocecal lymph node clearance. This is also required for tumors in the appendix base, as they may originate in the colon, and have a more malignant behavior with increased risk for local recurrence. For tumors 1–2 cm in size hemicolectomy is recommended in the presence of invasion of the mesoappendix or beyond, lymph node metastases, or tumor at the resection margins. If a similar sized lesion is confined to the appendiceal wall, guidelines suggest appendectomy is sufficient as there is a low risk for metastases. However, although the evidence base is lacking, a hemicolectomy may be recommended if histology suggests angioinvasion, high Ki67 index, or high mitotic index [22, 34, 35]. Follow-up may be considered in these circumstances and a rise in serum chromogranin A may support an extended operation. Few patients have lymph node metastases (3.8%), and distant metastases are rare (0.7%). Patients with regional metastases have 84% 5-year survival, while ~33% of patients with distant metastases survive ~5 years [36].

Goblet Carcinoid (Adenocarcinoid)

A more aggressive type of appendiceal carcinoid has mixed endocrine and exocrine (adenocarcinoma) features, and has been named adenocarcinoid, goblet cell carcinoid, or atypical appendiceal carcinoid [1, 22, 34, 35]. These tumors are less well circumscribed, diffusely infiltrating the appendix, and sometimes present with appendicitis. They are more malignant than the common appendiceal carcinoids, and often have intraabdominal metastases to the peritoneum and ovaries, sometimes appearing as a mucinous adenocarcinoma. The tumors do not express somatostatin receptors, and cannot be visualized by Octreoscan. Special histological markers may be used to identify the lesions [37]. This aggressive tumor entity should be treated with a right hemicolectomy and lymph node clearance, in combination with chemotherapy. For those with tumor spread, an aggressive surgical resection including oophorectomy and peritonectomy may be required [22].

Colon Carcinoids

Colon carcinoids are rare, representing ~8% of gastrointestinal carcinoids, and <1% of colon neoplasms [1, 2, 22, 38, 39]. They occur at ~65 years of age, with occasional tumors reported in children. Most tumors (48%) occur in the cecum, a minority originate in serotonin-producing EC cells similar to jejunal carcinoids [3, 22].

Less than 5% are associated with the carcinoid syndrome, which does not occur with distal colorectal carcinoids. The majority appear aggressive with less well-differentiated features, and tend to be large, ~5 cm, and exophytic when detected. These tumors have a higher proliferation rate, regional lymph node metastases are common, and there is a high incidence of liver metastases. Symptoms are similar to colon adenocarcinoma with typical malignant features of pain, a palpable abdominal mass, and occasionally occult bleeding. Tumors of the right colon may be larger when detected, than those of the left colon, and may cause obstruction. Occasionally tumors have been encountered in patients with colitis or Crohn's disease.

Diagnosis. Approximately 50% are asymptomatic and incidentally detected at colonoscopy. Right-sided lesions are rarely positive on somatostatin receptor scintigraphy. CT is used to evaluate local tumor extent and spread with liver metastases.

Surgical treatment. Although it has been suggested that small tumors confined to the mucosa can be locally excised, it appears wise to treat the majority with hemicolectomy and lymph node clearance. Due to their slow growth, palliative tumor debulking is recommended as for midgut carcinoids. Patients with colon carcinoids (but not patients with rectal carcinoids) have a slightly increased risk of synchronous colon carcinoma and should be investigated with a full colonoscopy at diagnosis. Overall 5-year survival is 40% and is mainly related to tumor stage.

Poorly Differentiated Colon Carcinoids

Poorly differentiated (small cell) neuroendocrine carcinomas with high Ki67 proliferation index occur in the right colon frequently associated with an adjacent adenoma or adenocarcinoma [3, 22, 40]. The tumors have generally metastasized at diagnosis, and are mainly treated with chemotherapy, but have a poor survival.

Rectal Carcinoids

The incidence of rectal carcinoids is rising, possibly due to increased colorectal cancer screening and comprise ~11% of gastrointestinal carcinoids [1–3, 22, 38–41]. They constitute 1–2% of all rectal tumors, being somewhat more common in Afro-Americans than in Caucasians, and occur at ~55 years of age [1, 22, 40]. Most commonly these tumors are found 4–13 cm above the dentate line on the anterior or lateral rectal walls. The majority appear as a solitary, typically yellowish, and submucosal polyp, <1 cm in diameter. These tumors have low incidence (0–3%) of regional lymph node metastases. Tumors 1–2 cm in size have ~4% of lymph node metastases and 7–34% distant metastases, which rises to ~46% when the muscularis is involved. Tumors >2 cm have metastases in 67–100% [39].

Diagnosis. The majority of rectal carcinoids <1 cm in size are found incidentally at endoscopy. Larger tumors may be associated with pain, change in bowel habit, and weight loss, but carcinoid syndrome is virtually never present.

Surgical treatment. Rectal carcinoids <1 cm are generally treated with excision biopsy and cauterization. They should be assessed preoperatively with transanal endosonography or MRI to assess muscularis invasion and regional metastases [39]. If these are absent transanal endoscopic mucosectomy (TEM) is justified. Presence of either favors a more aggressive excision, generally by anterior resection and regional lymph node clearance. This is also recommended for tumors >2 cm without general dissemination. Local tumor removal may be indicated in presence of systemic metastases. Patients with tumors >2 cm should be assessed with CT or MRI to visualize liver metastases. Octreoscan is rarely positive with rectal carcinoids due to lack of somatostatin receptors. Chromogranin A is not elevated and not valuable as tumor marker or diagnostic tool.

Overall 5-year survival for patients with regional metastases is ~45% and with distant metastases <20%.

Liver Metastases

The presence and extent of liver metastases is a major prognostic indicator in carcinoid patients. Many reports have described an improved quality of life and extended survival after medical and surgical treatment of liver metastases [1, 22, 28, 33, 42–46]. Aggressive treatment is especially indicated in presence of the carcinoid syndrome.

Therapeutic options include medical treatment with somatostatin analogues and interferon, chemotherapy in some tumor entities, liver surgery, radiofrequency ablation (RFA), liver embolization, treatment with radiolabeled somatostatin analogues, and in carefully selected patients liver transplantation [28].

The results of transplantation appear to be better in patients with less-extensive liver involvement. Transplantation requires careful case selection since the midgut carcinoid has a great tendency to recur.

Liver Surgery

Patients with carcinoid liver metastases should be evaluated for surgical resection or ablation to reduce tumor burden and to alleviate hormonal symptoms. Many have miliary spread, bilateral liver metastases, and are best treated with medical therapy or embolization. For patients with large, dominant lesions considerable long-term symptomatic relief and improved quality of life may be achieved by liver surgery, which can sometimes be performed concomitant with intestinal resection [1, 22, 28, 33, 42–47]. Surgery may consist of hepatic lobectomy or informal parenchyma-saving liver resections, combined with wedge resection or enucleation of smaller lesions. Recent refinements of surgical techniques, and two-stage liver resection combined with portal embolization, have reduced operative risks and the danger of liver insufficiency. Previously a 90% reduction of the mass of metastases was considered necessary for successful liver resection. Recently it has become evident that debulking less than this may also be beneficial, but outcome is poorer in patients with more than 50% liver involvement, or with rapidly proliferating lesions [1, 22, 28, 33, 42–47]. Five-year survival of $\geq$70% has been reported after apparently curative surgery, and symptom palliation has also been obtained with noncurative resections. However, virtually all patients will recur with further metastases following liver resection or ablative therapy, if follow-up is long enough.

Radiofrequency Ablation

RFA can induce coagulation necrosis of liver metastases of up to 4 cm in size, by applying alternating radiowave-length current via a needle introduced under ultrasound guidance [1, 48–51]. RFA can be performed at open surgery, at laparoscopy, or repeatedly as a percutaneous ultrasound-guided procedure. It may be combined with open surgery, for concomitant removal of larger tumors, and has increased the treatment options for bilateral liver metastases. An initial evaluation of metastatic spread is best achieved at open surgery, and this may be an important assessment of suitability for successful RFA treatment. Larger liver metastases may be coagulated with overlapping treatments, or by reducing the hepatic circulation during ablation, with hepatic artery clamping during surgery, or concomitant embolization during percutaneous RFA. The efficiency is related to the size of the tumor and distance to larger vessels [1, 50, 51]. Complication rates of RFA are generally $\sim$5%. Central bile ducts may be injured during treatment of tumors in the hepatic hilum. The effects of RFA on symptom palliation and efficiency of tumor removal need to be further evaluated.

Liver Embolization

Liver tumors usually have an arterial supply, and obstruction of these vessels will cause tumor ischemia. Liver embolization is considered an efficient method of inducing tumor regression and obtaining symptom control [1, 52–55], benefiting approximately 50% of carcinoid patients during a median of 7–14 months, with a reduced requirement for somatostatin analogues and improved effects of interferon treatment. Sequential and repetitive embolizations are of value for multiple and bilateral metastases. Recurrence after liver surgery has been treated by superselective embolization.

Embolization is generally contraindicated if tumor burden relative to normal liver parenchyma exceeds 50%, and in patients with signs of hepatic insufficiency. Morbidity and even mortality occur in $\sim$5%, but may be reduced in the hands of an experienced interventional radiologist. A “postembolization” syndrome including transient elevation of liver enzymes, 2–3 days of fever, nausea, and abdominal pain that typically lasts a week, is common. Chemoembolization, implying arterial embolization combined with intraarterial infusion of chemotherapy, may increase efficiency, but has generally not been considered for the common midgut carcinoids

due to the typical low proliferation rate and poor response to chemotherapy.

Liver Transplantation

Because of the generally slow tumor progression, liver transplantation may have a role for patients with carcinoid tumors [1, 56–60]. The role of liver transplantation versus medical therapy remains uncertain, because of the fear that immunosuppression may reduce survival. A metaanalysis revealed an approximate 50% 1-year survival and 24% 5-year disease-free survival, for patients with endocrine tumors following transplantation [56]. Carcinoids have a more favorable survival (69% at 5 years) than endocrine pancreatic tumors. Recent results indicate a reduction in operative risks and improved survival following transplantation for neuroendocrine tumors: ~77% 1-year tumor-free survival, 90% overall 5-year survival, but only ~20% 5-year tumor-free survival [57–60]. Limited tumor burden (<50% of liver volume) is more favorable for consideration of transplantation. Patients should have extraabdominal metastases excluded with imaging such as Octreoscan and 5-HTP PET. Ki67 proliferation index of <5% and an absence of markers demonstrating an aggressive tumor, have generally been required [60]. The transplanted liver frequently becomes a site for new metastases. Indications for transplantation must be balanced against the favorable results of medical treatment, and the proven tenacity of carcinoid tumors, which makes recurrence likely or inevitable.

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