Medical and Surgical Treatment of Parathyroid Diseases

An Evidence-Based Approach

Brendan C. Stack, Jr.
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Editors

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I wish to dedicate this effort to the many people who have significantly impacted my life and career, making this book possible.

I wish to thank my wife Cynthia L. Albright Stack for her tireless love and support of my career since the beginning of my internship and for the last 27 years. I also am thankful for the support, love, and inspiration from our seven children Brendan III, Mallory, Cameron, Madison, Meridith, McAllister, and Preston. You all have been splendid children.

I thank my parents Brendan C. Stack, Sr., DDS, MS and Marilyn K. Stack Lutz. My parents afforded me every opportunity available to me to pursue my education and expand my horizons in life in many other ways. Thank you so very much.

I am grateful for all of my teachers who have been so impactful upon my pursuit of knowledge. Specifically I wish to acknowledge those who made such a meaningful impact that has endured over the last four decades. They include, in chronologic order of my education:

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- *Mark J.Rowe, Ph.D., Retired Professor of Food Science and Nutrition, Brigham Young University, and formerly Professor of Biochemistry, Eastern Virginia Medical School.*
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Brendan Curran Stack, Jr., M.D., F.A.C.S., F.A.C.E.

I would like to dedicate this book to my wife Ann Riggs, my daughters Dana and Kaitlyn, and my parents Don and Shirley. Without their love and support this book and other achievements would not have been possible. I would also like to thank the students and residents I have worked with over the years. They have forced me to constantly strive to remain informed and up to date. I would also like to acknowledge the support of the endocrine faculty at the University of Rochester, particularly Dr. Paul Woolfe, Dr. Steve Wittlin, and Dr. Larry Jacob who were invaluable friends and mentors when I first started my career.

Donald L. Bodenner, M.D., Ph.D.

Foreword

Parathyroid diseases comprise various different entities that may be easily surgically cured, for example in the case of a typical imaging-positive hypercalcemic single neck parathyroid adenoma, but need extensive interdisciplinary knowledge and cooperation in the case of multiglandular disease, parathyroid cancer, ectopic location, or re-operative setting. This book is well constructed and comprehensive and presents current summary of endocrinology and surgical aspects of parathyroid diseases including parathyroid anatomy, physiology, and embryology, medical treatment for hyper- and hypoparathyroidism, parathyroid imaging, recent surgical techniques for conventional and endoscopic parathyroidectomy, and a final section of chapters on special topics which are highly informative for the parathyroid specialist.

The editors of this text have employed many of the world leaders in parathyroidology to create in-depth evidence-based summaries of the principles of the disturbed parathyroid-related calcium homeostasis in sporadic and hereditary, pediatric and adult parathyroid disorders. During the past decade, diagnosis and treatment of parathyroid diseases have been revolutionized by various molecular genetic, imaging, intraoperative, and surgical techniques. This text therefore comes at an appropriate time. It will serve as an excellent reference guide for a wide range of endocrinology and surgical experts involved in the interdisciplinary diagnosis and treatment. Although the fund of information is related to clinical management, the chapters are succinct and concise, making them highly valuable not only for clinicians but also for those involved in preclinical, molecular, and laboratory, as well as in postsurgical evaluation of patients. Overall, this book is really an outstanding resource for an evidence-based, yet individualized, management of parathyroid diseases and should have an active place in the current library of all physicians dealing with parathyroid patients.

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Preface

The concept of this book started after one of the editors (BCS) completed a monograph entitled *Parathyroids* for the Otolaryngology Clinics of North America in 2004. That rewarding experience, combined with a busy parathyroid practice while he was working at Penn State Milton S. Hershey Medical Center, planted the seeds of a larger parathyroid text in the mind of Dr. Stack. In 2005, Dr. Stack moved to the University of Arkansas for Medical Sciences (UAMS) where he immediately partnered with Donald Bodenner, M.D., Ph.D., a world-class thyroidologist and ultrasonographer, in forming a thyroid and parathyroid center of excellence. This partnership has continued for 11 years and has been very productive in both scholarly research and clinical production. The nascent idea for a parathyroid text conceived over a decade ago resulted in the present text as a result of the strong collaborative relationship between Drs. Bodenner and Stack and their mutual interest in caring for patients that suffer from parathyroid diseases.

We saw a need for a unique approach to writing a textbook about parathyroid diseases that existed in the present marketplace. Most parathyroid books/texts at the present time cater either to a medical or surgical audience. We thought a text with broader appeal might encourage an interdisciplinary approach to this sometimes complicated and vexing set of diseases. With this in mind, we set out to organize an encyclopedic work on parathyroid diseases. This would draw upon recognized experts from all related medical disciplines from across the globe. It would be organized in an evidence-based format both for reader ease in accessing best practices and understanding but would also mark the frontiers of the medical profession's knowledge of these diseases so as to lead the way for future research and exploration.

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Part I

Introduction

Evidence-Based Medicine

1

Adam P. Vasconcellos and Jennifer J. Shin

Contents

Introduction

Evidence-based medicine (EBM) and the development of best practice guidelines empower the modern physician to deliver high-quality care to his or her patients. EBM fosters the diagnosis and treatment of disease according to the strongest scientific evidence, and has the potential to not only improve clinical outcomes but also lower health care costs [1–4]. Evidence-based protocols have shortened duration of intensive care unit and overall hospital stay [4], reduced rates of central venous catheter-associated bloodstream infections up to 66 % [2], and stimulated the alcohol-based hand sanitizer intervention to curtail spread of multi-drug-resistant organisms in hospitals [5]. In fact, some argue that "evidence-based medicine has come to define what is rational in medical practice, with implications for both standardization and reimbursement" [3]. Concurrently, factors such as expanding performance measures [6] and the growth of accountable care organizations have cemented clinical research and evidence-based medicine as "a necessity for practitioner autonomy and economic survival" [7]. Certainly as the landscape of physician reimbursements shifts toward pay-for-performance, accessibility to and an understanding of best practice guidelines are essential to any clinician.

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Outcome Measures

An acronym previously set forth to highlight the anatomy of a study is "PICO" ("patients," "intervention," "comparison/control," "outcomes") [8]. EBM is shaped by the outcome measures of these individual studies. Some outcomes can be measured directly, such as recurrence of hyperparathyroidism after single-gland parathyroidectomy. Others require surrogate end-points, ideally translatable to patient-oriented outcomes, such as hoarseness (e.g., with evidence of vocal cord dysfunction on laryngoscopy or hypoparathyroidism on postoperative laboratories). The exactness by which an outcome measure is defined is similarly variable. For example, the outcome of "5-year survival" leaves little room for interpretation, whereas an outcome measure such as "multigland disease" merits further definition (i.e., as evidenced by ultrasound, ultrasound, and Tc99m-sestamibi scan, or bilateral neck exploration). As one group asserts, "precisely measuring an outcome permits the study results to be understood with complete certainty, maximizing their utility for a clinician attempting to apply them to his or her practice" [9].

Confounders and Bias

The goal of any study is essentially to examine the relationship between cause (the described intervention or variable) and effect (the outcome of interest). An ideal study establishes an effect as a direct result of a singular cause. However, in virtually all studies, secondary factors exist that may influence the outcome of interest, and these are evaluated as potential confounders. For example, consider a study that seeks to examine the impact of topical anesthetic on postoperative pain. Factors such as surgical expertise, systemic anesthesia, and extent of surgery could also influence the outcome of interest. In order for an appropriate cause-and-effect relationship to be determined, these potential confounders would have to be eliminated or at least accounted for. This is often best accomplished via randomization. With randomization, confounders can be similarly distributed among the different test groups, and the described intervention (e.g., use of topical anesthetic) is thereby isolated [9].

A study must similarly guard against all forms of bias, or errors in study technique that can artificially influence results. While bias in a study certainly does not imply an investigator's purposeful attempt to manipulate study results, it is important to be on guard for the many types of bias that can compromise study design and execution. Tables 1.1 and 1.2 detail different types of bias that can impact clinical trials and observational studies, respectively.

Levels of Evidence and Grading of Recommendations

When determining what is "best evidence," the most rigorous study designs are, by nature, those least prone to errors from chance, confounding, and bias. Table 1.3 illustrates how study design directly contributes to a study's position within the hierarchy of evidence. It should be noted that this tier system for assigning proportionate value to study design is by no means absolute; a flawed randomized control trial, for example (e.g., with inherent bias, poor design or control of external variables), would certainly not hold the same weight as a rigorously designed and executed study. Rather, this is to serve as a rough outline for how practitioners should approach impact of study design, and how committees who review available data establish guidelines and clinical recommendations.

Levels 1a and 1b involve randomized controlled trials, "the gold standard in study design." As described above, randomized controlled trials provide the best opportunity to establish direct causation of an intervention arm on an outcome measure by most actively controlling for potential confounders. Recommendations based upon level 1a and 1b data are considered grade A recommendations. A summary of the evidence-based grading system is below in Table 1.4. It should be noted that it is reasonable to make clinical recommendations based upon any study level, but only when higher levels of evidence are unavailable.

Table 1.1 Bias in clinical trials

Timing of bias	Type of bias	Explanation
Before a clinical trial begins	Selection bias	Study subjects improperly chosen
	Channeling bias	Prognosis of study subject influences group or cohort assignment
During a clinical trial	Interviewer bias	Variability in manner by which information is gathered or recorded from subject to subject
	Chronology bias	Comparison group includes historical controls
	Performance bias	Exposure to other factors apart from intervention
	Recall bias	Variability in accuracy of subject retrieval of prior experience
	Attrition (Transfer) bias	Excess study subjects lost to follow-up
After a clinical trial	Detection bias	Partiality when assessing outcomes
	Expectation bias	Expecting a certain result can influence assessment of outcomes
	Correlation bias	Correlation improperly implied as causation
	Publication (Citation) bias	Favor distribution of studies showing a difference between groups as opposed to studies supporting null hypothesis

[3, 10]

Table 1.2 Bias in observational studies

Type of bias	Explanation
Self-selection bias	Social, cultural, linguistic, and health values or barriers may promote or hinder patient enrollment in a study, screening program, or measured point of care
Lead-time bias	Influence of a screening program on calculation of stage-specific survival rates: patients living in areas with a screening program for disease X may be diagnosed earlier and therefore concluded to live longer with disease X than age-matched counterparts living in an area without a screening program
Ecological fallacy	Assumption that observed associations can be extrapolated from a population to an individual
Exclusion bias	Evaluating data leaving a particular group or groups out of a sample population
Referral bias	Influence of referral from primary to tertiary and subspecialty centers on makeup of a study population: an observational study consisting of a patient population from a tertiary or subspecialty clinic may have higher percentage of complex or severe cases and adverse outcomes
Spectrum bias	Change in the performance characteristics of a particular test when applied to different patient subgroups

[10, 11]

To aid in the development of clinical guidelines or recommendations, medical groups and societies have relied on systematic reviews and meta-analyses to evaluate the body of available data on specific clinical questions. In this way, a systematic review incorporates a "statistical pooling of data" to provide an estimate of the true effect of an intervention tested across, at times, many studies [9]. For the busy clinician, systematic reviews are invaluable. They analyze and place value on data with an end goal of translating a potpourri of studies and medical literature into actionable clinical practice guidelines. In this way, evidence-based guidelines are created by multidisciplinary teams and/or professional organizations.

Table 1.3 Levels of evidence

OCEBM level	Therapy/prevention, etiology/harm	Prognosis	Diagnosis	Differential diagnosis/ symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity) of RCTs	SR (with homogeneity) of inception cohort studies; CDR″ validated in different populations	SR (with homogeneity) of level 1 diagnostic studies; CDR″ with 1b studies from different clinical centers	SR (with homogeneity) of prospective cohort studies	SR (with homogeneity) of level 1 economic studies
1b	Individual RCT (with narrow confidence interval)	Individual inception cohort study with >80 % follow-up; CDR″ validated in a single population	Validating cohort study with good reference standards; or CDR″ tested within one clinical center	Prospective cohort study with good follow-up	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none	All or none case series	Absolute SpPins and SnNouts	All or none case series	Absolute better-value or worse-value analyses
2a	SR (with homogeneity) of cohort studies	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity) of level >2 diagnostic studies	SR (with homogeneity) of 2b and better studies	SR (with homogeneity) of level >2 economic studies
2b	Individual cohort study (including low-quality RCT; e.g., <80 % follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; derivation of CDR or validated on split-sample only	Exploratory cohort study with good reference standards; CDR after derivation, or validated only on split-sample or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	Outcome research; ecological studies	Outcome research		Ecological studies	Audit or outcome research
3a	SR (with homogeneity) of case–control studies		SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies

3b	Individual case–control study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor-quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations
4	Case series (and poor-quality cohort and case–control studies)	Case series (and poor-quality prognostic cohort studies)	Case–control study, poor or non-independent reference standard	Case series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Adapted from Howick et al. [12]
Abbreviations: *OCEBM* Oxford Center for Evidence-Based Medicine, *RCT* randomized controlled trial, *SR* systematic review, *CDR* clinical decision rule

Table 1.4 Evidence-based grading system

Grade	Description
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies, or extrapolations from level 1 studies
C	Consistent level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence only, or inconclusive evidence from any level

Adapted from Howick et al. [12]

Expert Opinion

The objective of this text is essentially to deconstruct and outline best practices for parathyroid medicine and surgery using the highest levels of evidence available. It should serve not only as a user-friendly guide for clinical practice, but also as a springboard for further investigation and research to hone what is now best evidence, but will someday be surpassed. It should also be noted that the promotion of clinical guidelines based upon the evidence does not supplant or undermine individual clinical judgment. As one group is quick to point out, "evidence based medicine is not 'cookbook' medicine" [13]. Rather, practicing evidence-based medicine involves "an integration of best available evidence with clinical judgment and the patient's wishes" [14]. Figure 1.1 illustrates the idea that clinical judgment ultimately determines whether a given set of recommendations and guidelines applies to an individual patient. Familiarity with the patient subsets, interventions, control maneuvers, and outcome measures ("PICO") that comprise the evidence to support best practice guidelines will help a physician to determine whether those guidelines actually apply to the individual patient and clinical scenario he or she encounters in the office. It is thus imperative for a clinician to understand the nuances and derivation of best practice recommendations.

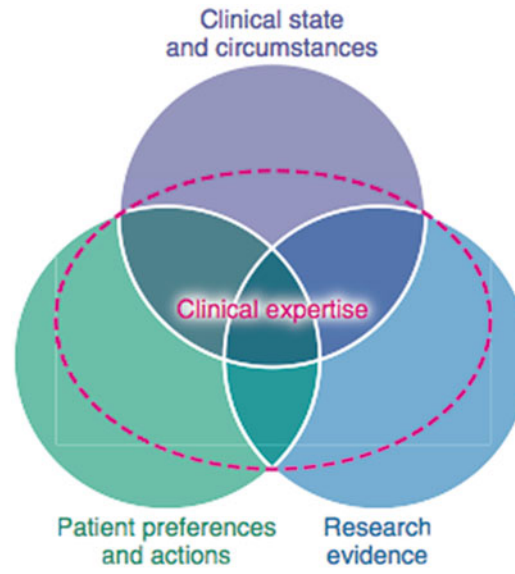

Fig. 1.1 Evidence-based clinical decision-making. Adapted from Haynes et al. [15]

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Evidence-Based Medicine: Approach and References Classification

2

Andrew M. Hinson and Brendan C. Stack, Jr.

I have neither the ability, knowledge, time, or space to classify all present-day therapies. All I feel capable of is a rough classification …

—AL Cochrane, 1971

Contents

Evidence-based medicine (EBM) is the process of systematically reviewing, appraising, and applying the best research available to preserve the quality of patient care [1]. In short, the process is daunting, tedious, and, by definition, never-ending. We are reminded of Sisyphus's eternal task of rolling a large boulder up an even larger hill only to watch the rock roll back down without ever reaching the summit [2]. We begin with two great advantages. First, the task is well defined—we need to only consider four (usually) small glands that reside (usually) in the human neck. Second, unlike Sisyphus, we need not carry the burden alone. While no single person possesses the ability, knowledge, time, or space to classify all present-day therapies, we may be able to accomplish a great deal if we work together.

The goal herein was to present a simple, practical, and informative framework that the authors of this textbook could follow in order to classify the quality of their supporting evidence. We systematically reviewed previous EBM classification schemes, appraised what worked best for our purposes, and compiled these findings into the following two tables [3, 4]. Table 2.1 involves assigning a categorical classification by article type (basic science, basic science review, clinical investigation, clinical review, or population/observational study) to the cited reference. Table 2.2 involves assigning an EBM level (1–5) and adjustment factor (a, b, c) to the reference.

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Table 2.1 EBM categorical classification of references

Article type	Definition
Basic science	Controlled experiment; independent variable affects a dependent variable in a laboratory setting
Basic science review	Review of basic science experiments
Clinical investigation	Controlled experiment; independent variable affects a dependent variable in a clinical setting
Clinical review	Review of clinical experiments or trials
Population/observational study	Draws inferences about a particular characteristic where the assignment of a treated and control group is outside the control of the investigator

Adapted from A Guide to Practitioner Research in Education by Menter et al. [3]. SAGE Publications Inc., Washington DC

Table 2.2 EBM level (1–5) and grade (A–C) classification of references

Level	Adjustment	Description
1	A	Homogenous prospective, randomized controlled trials (RCT) or basic science (BS) with controls
	B	One prospective RCT or BS experiment supporting hypothesis
	C	Heterogeneous or mixed results from >1 RCT or BS experiment
2	A	Homogenous non-RCT with controls
	B	One non-RCT with controls
	C	Heterogeneous or mixed results from >1 non-RCT with controls
3	A	Homogenous observational studies without controls
	B	Heterogeneous observational studies without controls
4		Small case series or case reports
5		Expert opinion or inconclusive evidence

Adapted from Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)

(In general, level 1 evidence is considered "better" than level 2, and level 2 is "better" than level 3, etc.) For further classification involving levels 1–3, an adjustment factor (a–c) was used to identify the level of agreement between studies (*a* suggests a higher level of agreement than, say, *b* or *c*, etc.).

Our EBM classification system is admittedly not perfect. However, we hope that it points the reader in the right direction, highlights the great work that has been accomplished already, and illuminates what lies ahead.

Expert Opinion

EBM classification has become the new standard of practice guidelines, consensus documents, and the peer-reviewed literature. It was the editors' hope that by adding the EBM classification framework to the organization of this text, we would extend this new standard to medical specialty texts and identify areas in the frontiers of our collective knowledge that are deficient in high levels of evidence.

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Part II

Parathyroid Anatomy, Physiology, and Embryology

Applied Embryology, Molecular Genetics, and Surgical Anatomy of the Parathyroid Glands

3

Andrew M. Hinson and Brendan C. Stack, Jr.

Contents

Introduction

The parathyroid glands are small (<50 mg) endocrine glands located on the posterior aspect of the thyroid gland. The primary function of the parathyroid glands is to produce and secrete parathyroid hormone (PTH), which regulates calcium homeostasis in the circulation. PTH deficiency (hypoparathyroidism) or excess (hyperparathyroidism) may be caused by mutations in genes required for parathyroid development or physiological function as well as other causes. As knowledge of the human genome increases, advances in diagnostic and treatment techniques for parathyroid-related disorders will undoubtedly involve a thorough understanding of the key molecular processes guiding parathyroid development and function. This chapter provides a review of these events, as currently understood, as well as their potential clinical relevance.

Organogenesis: Morphogenesis and Differentiation

Six pairs of pharyngeal arches, transient bulges appearing on the lateral surface of the embryonic head, appear around the fourth week of gestational development [1]. Each arch contains a core of mesenchymal tissue encapsulated externally

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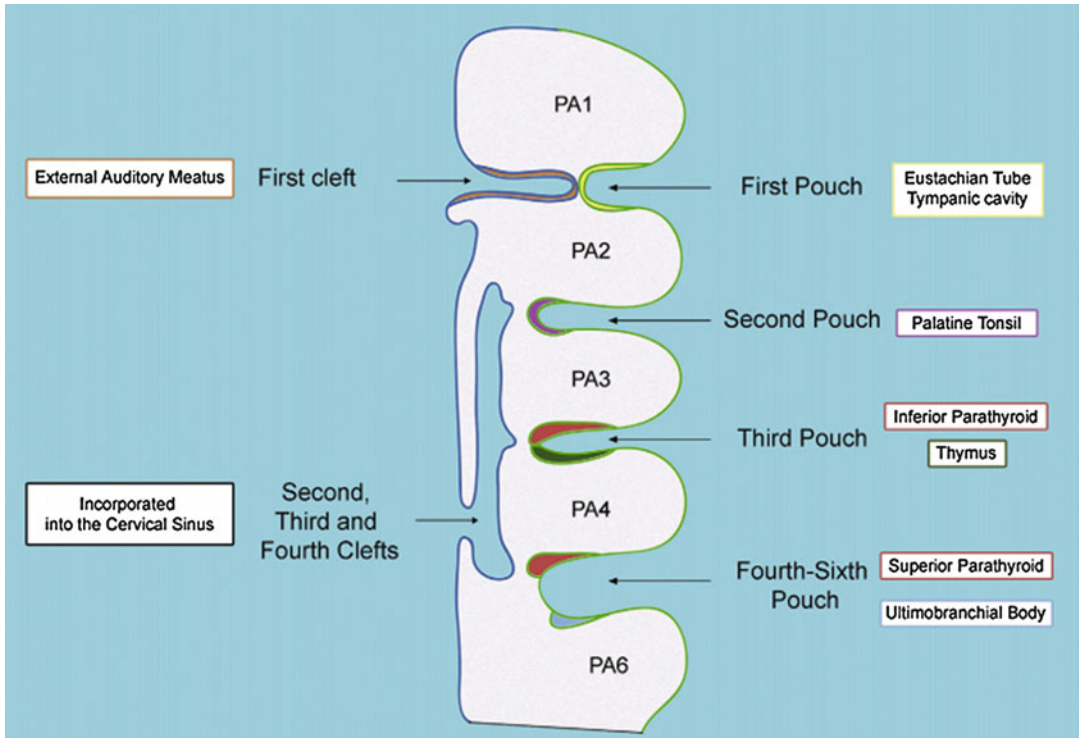

Fig. 3.1 Formation of the pharyngeal pouches and their corresponding derivatives. From [2]. *PA* pharyngeal arch

by ectoderm and internally by endoderm [1]. During embryogenesis, the endoderm and ectoderm invaginate toward each other forming a series of ectodermal-lined depressions, called pharyngeal clefts, and endodermal-lined outpockets, called pharyngeal pouches (Fig. 3.1; [2, 3]).

These endodermal outpockets contact the surface ectoderm at precise sites along the anterior–posterior axis of the pharyngeal apparatus, and they expand along the dorsoventral axis to generate their characteristic narrow, slit-like shape [4, 5]. The two most cranial pouches, 1 and 2, form first followed by pouches 3 and 4 [4, 6]. The parathyroids glands develop from the most caudal pouches, but the number of glands varies depending on species [3]. In humans and birds, two sets of parathyroids (from the third and fourth pouches) develop, while only one set (from the third pouch) forms in rodents [3]. In humans, the epithelium of the dorsal surface of the third pouch differentiates into the inferior parathyroid glands, while the ventral surface differentiates into the thymus [2]. The epithelium of the dorsal wing of the fourth pouch differentiates into the superior parathyroid glands, while the ventral wing differentiates into the ultimobranchial body (Fig. 3.1; [7, 8]).

Using murine and chick-quail models, much progress has been made in identifying specific transcription factors (*Hoxa3-Eya1-Pax1/9-Six1/4* and *Tbx1)* and signaling molecules (*Bmp4, Fgf8, Shh, Wnt5b*) involved in the early formation and patterning of the third and fourth pouches [9–11]. The pouches are highly polarized structures delineated into precise molecular domains [4, 6, 12, 13]. In the third pouch, the epithelial cells express either *Gcm2*, destined to become parathyroid tissue, or *Bmp4* and *Foxn1*, destined to become thymus [10, 12–14]. In the chick, *Gcm2* is expressed in both the third and fourth pouches, supporting parathyroid development from both of these pouches [11]. Of note, *Gcm2* is not required for early third pouch patterning into thymus/parathyroid domains, but appears to be

required for later parathyroid differentiation and survival [13]. Thus, the organ-specific cell types are already established even before expression of *Gcm2*, as indicated in the thymus by immigration of lymphocyte progenitors and in the parathyroid by expression of PTH, P75NTR, S100 protein, and chromogranin A [7, 13, 15]. The primary induction cue that defines whether the third pouch precursor cells are destined to become parathyroid or thymus remains unknown [10, 13].

In humans, a number of hypoparathyroid developmental anomalies have been investigated, revealing important roles for particular genes involved in early third and fourth pouch morphogenesis. In DiGeorge syndrome (DGS), there is congenital failure in the development of the third and fourth pouch derivatives with resulting hypoplasia or agenesis of the parathyroid glands and thymus [8]. These patients may present with a range of findings: hypoparathyroidism with hypocalcemia, immune deficits secondary to lack of T-cell function, cardiac defects including truncus arteriosus, and characteristic facies [16]. Microdeletions mapped to chromosome 22q11.2 (referred to as DGSI) have been described in up to 90 % of these patients [8, 16]. At present, the gene thought to be responsible for DGSI is *TBX1*. *TBX1* is a T-box transcription factor that is expressed in highly regionalized domains during early pharyngeal development. In murine models, *Tbx1* mutants have markedly decreased expression of *Gcm2*, suggesting that this parathyroid-specific marker is one of the downstream targets of the DGS1 gene [8].

Similarly, abnormal expression of *GCM2* has been identified in other parathyroid-related disorders. Homozygous inactivating mutations in *GCM2* have been described in human familial autosomal recessive and dominant forms of isolated hypoparathyroidism. These individuals may have undetectable PTH serum levels. It is not yet clear whether the parathyroids are unformed or hypoplastic in this population [17, 18]. In addition, there have also been reports of parathyroid adenomas associated with deregulated (both elevated and reduced) expression of *GCM2*. At present, the clinical significance of these findings remains unclear [19, 20]. In any case, this transcription factor required in both differentiation and ultimate survival of the parathyroid glands is providing new insights into how the parathyroid gland forms and functions.

Separation from the Pharynx

The inferior and superior parathyroid glands detach from the pharyngeal wall around the end of the fifth gestational week [21]. The mechanism by which the thymus and parathyroid primordia detach from the pharynx has been extensively studied using murine models [22]. Early in development, the site of pharyngeal attachment is shared equally between the *Gcm2*+ parathyroid and *Bmp4*+ thymus domains [7, 22]. Neural crest cells, surrounding the pouches, express molecular signals that define the border location and size of the two molecular gradients [7]. Preferential proliferation of the thymus primordium relative to the parathyroid primordium, however, results in a dramatic increase in size and caudal growth of the thymus [23]. This unequal growth pattern results in the parathyroid domain, located on the cranial portion of the thymus, being displaced from its pharyngeal attachment [24]. Thus, the thymus persists as the sole connection to the pharynx [7, 22]. Apoptotic epithelial cells have been identified at the final attachment site, suggesting that separation is mediated by programmed cell death. The molecular signaling pathway directing this site-specific apoptosis remains elusive. However, recent evidence suggests that low levels of FGF signaling, which is associated with cell-mediated death in several other developmental contexts, may be involved [22].

Separation from the Thymus

A number of mutations in both the neural crest and endoderm have been associated with delayed thymus and parathyroid separation, suggesting that the interaction between these two cell types is key [14, 23–25]. During embryogenesis, the pharyngeal organs, especially the thymus, are densely surrounded by mesenchyme derived from the neural crest [26]. Recent evidence sug-

gests that the neural crest mesenchymal cells migrate in between the *Bmp4*+ and *Gcm2*+ epithelial domains and act as a physical "wedge" separating the two zones [14].

Based on observations in both mice and humans, separation is frequently incomplete [27, 28]. In murine models, using high-resolution in situ hybridization, the *Gcm2*+ parathyroid domain shows a relatively high tendency to fragment and leave small parathyroid clusters either attached to or trailing the thymus into the mediastinum [7, 27]. It is thought that the generation of these microscopic parathyroid clusters is the source of supernumerary or accessory parathyroid tissue [7, 27]. In humans, the prevalence of supernumerary glands is between 2 and 6 % [29], and as many as 11 glands have been reported in large autopsy series [28, 30]. In 2/3 of cases, the fifth gland is inferior to the lower pole of the thyroid associated with the thyrothymic ligament or the thymus. The remaining third of supernumerary glands are typically adjacent to the thyroid between the orthotopic superior and inferior parathyroids [30].

A number of studies have suggested that the thymus, which shares such an intimate origin with the parathyroid gland, may serve as an auxiliary source of PTH [27]. In murine models, extra-parathyroid PTH production has been reported from misplaced, isolated parathyroid cells that were most commonly still attached to the thymus [27]. In addition, medullary thymic epithelial cells express PTH in a *Gcm2*-independent manner as a means for self-selection [27]. However, at present, it does not appear that these medullary cells provide any auxiliary endocrine function and the clinical significance remains elusive [27]. Instead, the generation of multiple, microscopic parathyroid clusters is the most likely source of any physiologically relevant "thymic PTH."

Migration

In humans, the inferior and superior parathyroid glands migrate inferiorly and medially until arresting on the dorsal side of the caudal thyroid lobes around the seventh week [31]. Migration of the pharyngeal derived organs has been particularly well characterized in murine models. Following detachment, the thymus/parathyroid primordium moves in a caudal-ventral-medial direction towards the anterior thoracic cavity [2]. During this time, the parathyroid domain remains attached to the cranial pole of the thymus [2]. When the thymus passes along the lateral sides of the thyroid, the parathyroids detach and remain adjacent to the thyroid [2].

The thymus, in contrast, continues its migration into the anterior mediastinum where it joins its contralateral thymic lobe [2]. Following separation of the parathyroids from the thymus, the parathyroids do not migrate any further caudally [7]. At present, there is no evidence that the parathyroids are able to migrate independently of the thymus lobes [7]. Interestingly, the parathyroids lack a well-defined mesenchymal capsule, which is thought to be the source of the migrating neural crest driving thymus migration [7]. The variable location of the inferior glands in the neck then is likely a consequence of wherever they separate from the thymus [7]. In humans, when no migration occurs, the inferior glands remain at the level of the third pharyngeal pouch, near the bifurcation of the carotid artery where it appears to be located higher (and more ventral) than its superior counterparts [21].

The long descent of the inferior parathyroid glands with the thymus from the neck into the anterior mediastinum is responsible for their highly variable location, which may be anywhere from the hyoid bone to the lower mediastinum (Fig. 3.2). In 50 % of cases, the inferior parathyroid gland may be found within 1 cm inferior, lateral or posterior to the inferior pole of the thyroid [28]. It is typically anterior to the coronal plane drawn along the recurrent laryngeal nerve. The recurrent laryngeal nerve courses around the fourth aortic arch in between the ventral side of the superior glands and the dorsal aspect of the inferior glands [32].

In a large autopsy series ($N=942$) including 3796 parathyroid glands, 324 glands (8.5 %) were ectopic. The most common sites for surgical exploration of ectopic inferior glands are anywhere

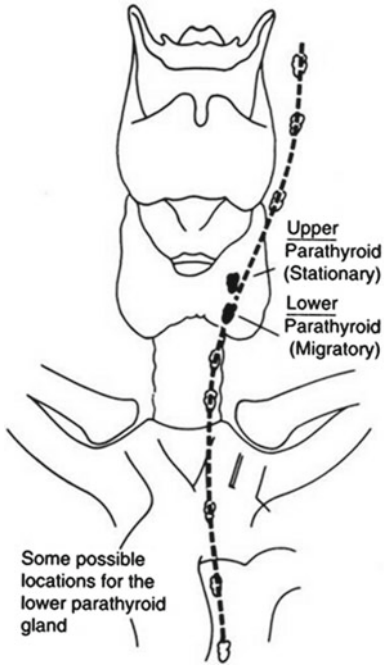

Fig. 3.2 Migratory descent of the inferior parathyroid glands during embryogenesis may result in highly variable anatomic location, which may be anywhere from the angle of the mandible to the pericardium. From http://www.thyroidmanager.org/wp-content/uploads/2011/06/35-8.png

along the common carotid artery, from the level of thyroid to the pericardium [29]. The most common ectopic location for an inferior gland is in the anterior mediastinum, representing some 5–6 % of ectopic cases [28, 29]. The glands are found in the upper mediastinum almost twice as frequently than in the lower mediastinum [29]. In young adults, the glands may be included in the lobular remnants of the thymic horns [21]. During embryogenesis, the inferior glands may also be displaced posterior and inferiorly resulting in their location along the recurrent laryngeal nerve on the lateral border of the esophagus. Further, rarely, they may be displaced posterior and laterally resulting in their unusual location in the upper posterior mediastinum [21].

The superior parathyroid glands have a more restricted migration. After detaching from the pharynx, they attach to the caudally moving thyroid, and remain in contact with the posterior midportion of the thyroid lobe. This limited course leads to more restricted anatomical variation relative to the inferior glands. In 85 % of cases, the superior gland may be located on the posterior aspect of the thyroid lobe in a 2-cm diameter circle centered 1 cm above the crossing of the inferior thyroid artery and the recurrent nerve [28, 30, 33]. In relation to the laryngeal framework, the superior glands are located at the level of the posterior ring of the cricoid cartilage [21]. The most common sites for ectopic superior glands are the upper pole of the thyroid lobe (usually in close proximity to the recurrent laryngeal nerve) and the upper vascular thyroid stalk behind the hypopharynx and cervical esophagus [29].

Occasionally, additional growth of the developing thyroid (pre- or post-natal) via enlargement of existing follicles may circumscribe the adjacent parathyroid and imbed them internally [34], resulting in the rare intrathyroid parathyroid (Fig. 3.3). The incidence of intrathyroidal parathyroid glands is poorly documented, but ranges between 0.7 and 6.7 % of ectopic glands [34, 35]. The wide variability in reporting is likely a reflection of whether the authors include parathyroid adenomas partially within the thyroid capsule or strictly limit the definition to those glands fully encased within the thyroid parenchyma [34] (Figs. 3.4 and 3.5).

Summary

The parathyroid glands are endodermal derivatives of the third and fourth pharyngeal pouches. Parathyroid organogenesis and morphogenesis are tightly regulated processes involving reciprocal molecular cross talk between all embryonic cell types: ectoderm, mesoderm, endoderm, and neural crest. Differentiation and survival of the parathyroid chief cells from pouch precursor cells involve highly regionalized expression of *Gcm2*, the earliest parathyroid-specific marker. Separation of the thymus, and consequently parathyroid glands, from the pharynx occurs via apoptosis, which is confined to discrete cellular domains. Neural crest-derived mesenchymal cells may be involved in separating the inferior

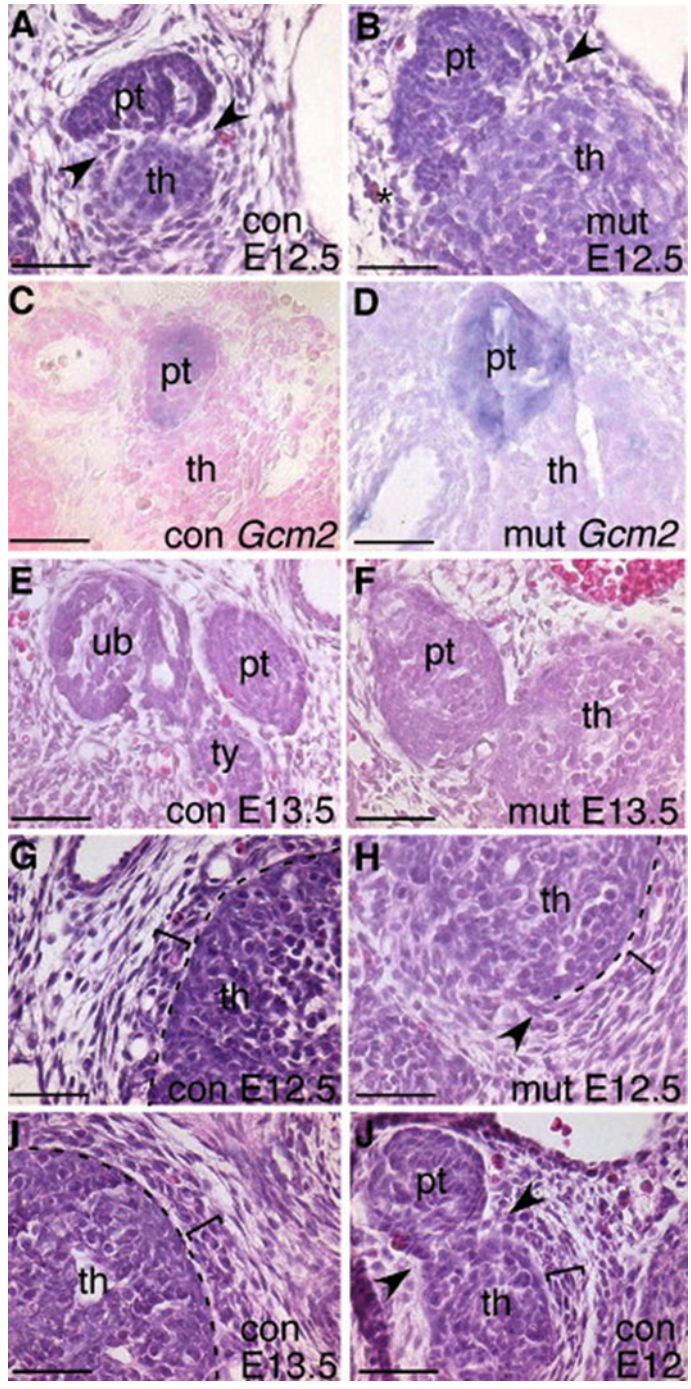

Fig. 3.3 Disrupted mesenchymal condensation and delayed separation of the thymus and parathyroid in Foxg1-Cre;Bmp4 mice mutants. (**a**, **b**, **g**, and **h**) H&E-stained transverse sections through E12.5 control (**a** and **g**) and Foxg1-Cre;Bmp4 mutant (**b**, **h**) embryos. (**c** and **d**) *Gcm2* expression at E12.5 in control (**c**) and mutant (**d**) embryos. (**e**, **f** and **i**) E13.5 transverse sections stained with H and E. At E12.5 and E13.5 the condensing mesenchyme (*bracket*) and thymus capsule (*dotted line*) are clearly evident (**g** and **i**). Part of the thymus capsule is missing in the mutant (H), coincident with adjacent mesenchymal disorganization (*arrow*). In controls at E12 and E12.5 (**j** and **a**), the mesenchyme at the site of parathyroid-thymus separation condenses to form "wedges" (*arrows*). (**b**) E12.5 mutant with some organization into a "wedge" on one side (*arrow*), but not on the other (*). *con* control, *mut* mutant, *th* thymus, *pt* parathyroid, *ub* ultimobranchial body, *ty* thyroid. Scale bars = 50 μm. Image and caption from [14]

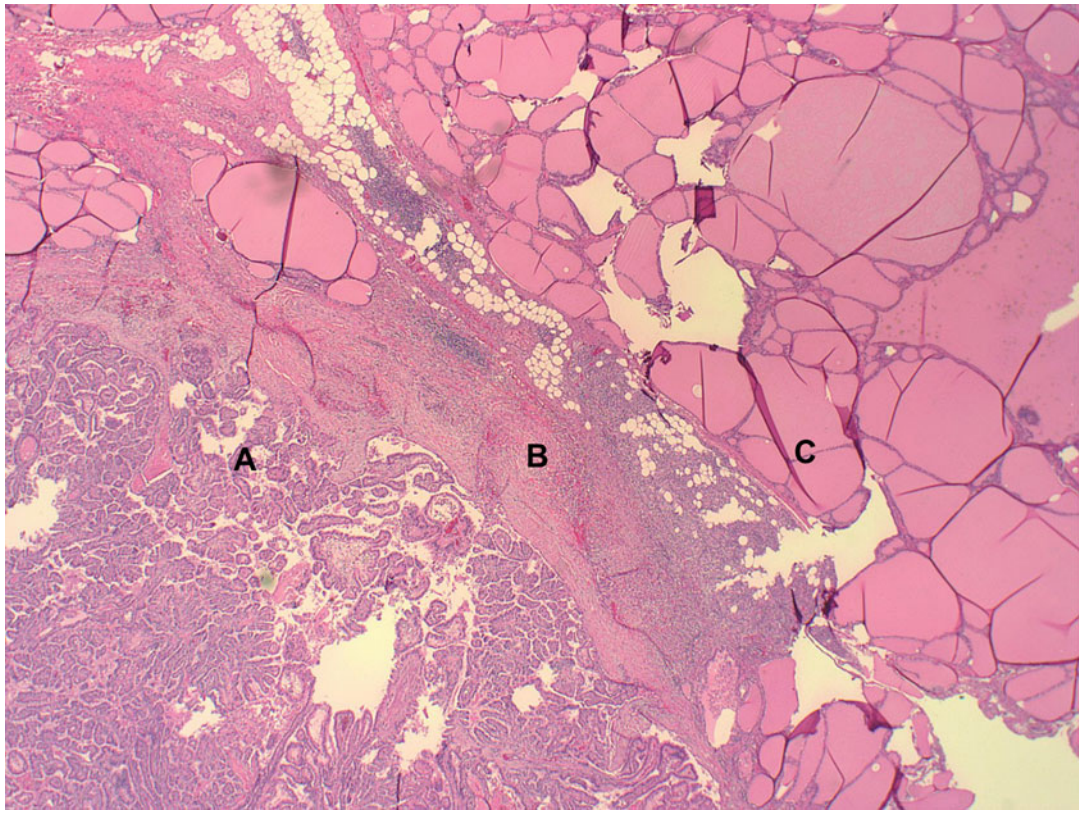

Fig. 3.4 Hematoxylin and eosin (HE) stain (4×) showing an intrathyroid parathyroid adenoma principal cells (*A*), fibrous capsule (*B*), and thyroid follicles (*C*). Photo courtesy of Dr. Chien Chen, Department of Pathology, UAMS

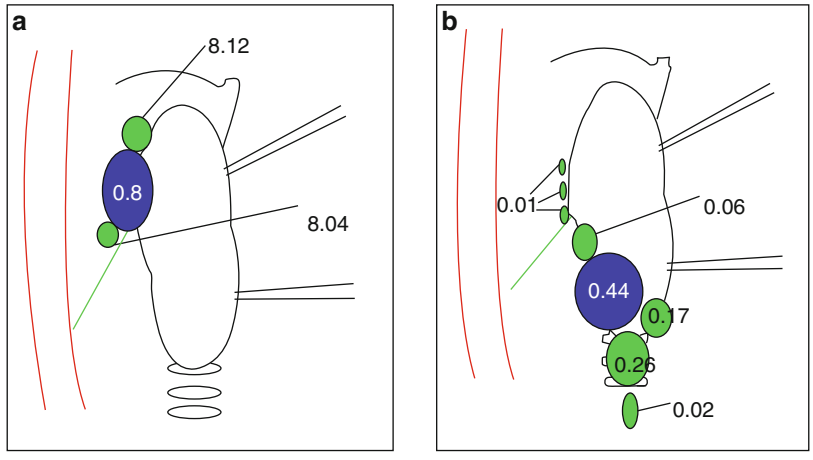

Fig. 3.5 Image credit to J. R. Jaglowski, MD. Numbers are % occurrence of the superior (**a**) and inferior parathyroid glands (**b**) in a given area

parathyroid glands from the thymus, as well as directing caudal migration of the glands to their final location on the posterior inferior aspect of the thyroid. The relatively long migratory descent of the inferior parathyroid glands is responsible for their highly variable anatomical location, which can be anywhere from the angle of the mandible to the pericardium (Fig. 3.1). Disruption in the organogenesis, morphogenesis, separation, and/or migration of the parathyroid glands results in both non-pathologic (ectopic) and pathologic aberrant anatomy and physiology later in life.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion

Familiarity with embryology often takes a back seat to gross anatomy and surgical experience for most parathyroid surgeons. This is unfortunate. A solid knowledge of embryology and its reported variations is essential for a successful surgical practice and critical for managing reoperative parathyroid patients.

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EBM Category/Level/Grade in Bold

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Parathyroid Physiology and Molecular Biology

4

Andrew M. Hinson and Brendan C. Stack Jr.

Contents

Introduction

The parathyroid hormone (PTH) gene has been sequenced in more than ten different species. Phylogenetic analysis has identified an array of homologous domains associated with the synthesis, secretion, and degradation of PTH. These studies are advancing our understanding of the molecular signaling and feedback mechanisms involved in the hormonal control of calcium and phosphate metabolism. This chapter reviews these physiologic processes at the molecular level, which serves as a solid conceptual framework for understanding the pathology discussed in later chapters.

Regulation of Gene Expression

Gene

The PTH gene is located on the short arm of chromosome 11 (11p15.3–p15.1) and consists of two introns and three exons [1–3]. The gene and encoded mRNA are nearly twice as long as the primary translated product, owing to the presence of lengthy untranslated regions (UTRs) flanking both ends. The three exons represent the functional domains of the mRNA and encode the following: exon 1 → 5′ UTR; exon 2 → signal peptide (25 amino acids); and exon 3 → PTH and 3′ UTR [4–6].

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Transcription and Regulation by Vitamin D

The UTRs possess significantly more genetic variability across species compared to the coding sequences. In the 5′ UTR, however, a number of conserved domains, known as functional response elements, have been identified and are instrumental in regulating transcription [6]. Perhaps the most significant of these clinically is the vitamin D response element (VDRE). $1,25(OH)_2D_3$, or calcitriol, is the biologically active vitamin D metabolite that binds and activates the vitamin D receptor (VDR) located in the parathyroid gland. The ligand-activated VDR interacts with a neighboring retinoic acid receptor (RXR) to form a heterodimer complex. VDR-RXR binds to the VDRE in the PTH gene promoter and downregulates transcription (Fig. 4.1). This model of vitamin D-dependent gene regulation is far from exhaustive. PTH transcription is also attenuated by an array of other regulatory coactivators and corepressors [7]. In addition, calcitriol also modulates PTH transcription by increasing (i.e., amplifying the inhibitory effect) or decreasing (i.e., dampening the inhibitory effect) the concentration of VDRs and calcium-sensing receptors (CaSR) in the parathyroid chief cells [8].

The relationship between calcitriol and PTH gene suppression has been used to prevent and treat secondary hyperparathyroidism in patients with renal failure [9]. Unfortunately, despite increases in dosing, up to 20–30 % of hemodialysis patients treated with a nonselective vitamin D receptor activators (VDRA) show no decrease in serum PTH levels [10]. The underlying mechanism causing resistance has been investigated in animal and human models [11, 12]. In rats with renal failure, the VDRs possess only half of the DNA binding capacity compared to their control counterparts. In addition, the incubation of normal VDRs in a uremic plasma ultrafiltrate results in more than a 50 % loss of VDRE binding sites. Uremic toxins may alter or destroy the DNA-binding sites resulting in an inadequate compensatory response following calcitriol administration [12].

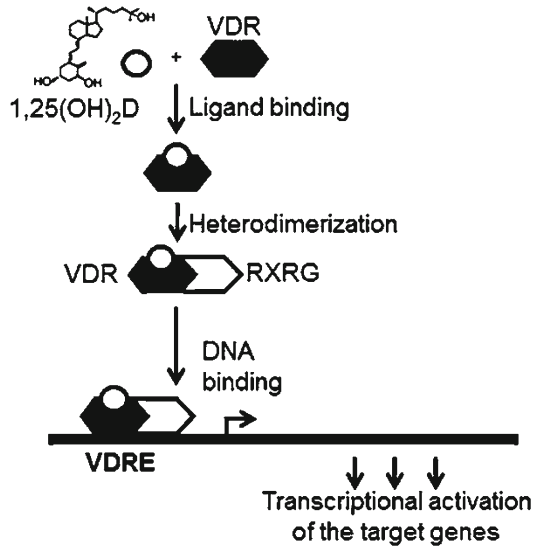

Fig. 4.1 Bioactive vitamin D activates the vitamin D receptor (VDR), which interacts with a neighboring retinoic acid receptor. This complex then binds to the vitamin D response element (VDRE) in the PTH gene promoter and downregulates PTH transcription. From: Vimaleswaran KS et al. Interaction between allelic variations in vitamin D receptor and retinoid X receptor genes on metabolic traits. BMC Genet 2014; 15:37

In humans, particular polymorphisms in the VDR gene (12q12.14) have been identified in patients with chronic kidney disease that may affect their response to intravenous calcitriol [10]. In general, a higher incidence of the *b* allele of the VDR BsmI gene has been reported in hemodialysis patients with secondary hyperparathyroidism [13]. In predialysis patients with mild-to-severe chronic renal failure, patients with the *BB* genotype have a greater reduction in PTH levels following administration of a single bolus of calcitriol, despite having corrected for calcium and phosphorous levels. The patients with *BB* genotype also show slower disease progression compared to patients with the *bb* genotype. The authors from this study concluded that patients with the *BB* genotype could remain on hemodialysis longer before requiring a parathyroidectomy [14, 15]. However, it is important to note that when the parathyroid gland specimens were removed from these patients, tissue culture analysis of PTH secretion patterns were not associated with the various VDR alleles and response

to calcitriol [15, 16]. Thus, at present, the current level of evidence does not support adapting treatment algorithms according to a patient's VDR allele status [10]. A challenge for the future will be identifying other transcription regulators and mechanisms that may serve as biomarkers or possibly even therapeutic targets to aid in the management of these patients.

Posttranscriptional Regulation by Calcium and Phosphate

The amount of PTH synthesized for translation is highly dependent on events occurring after transcription (Fig. 4.2). For example, dietary-induced hypocalcemia results in a ten-fold increase in PTH mRNA levels via posttranscriptional processes alone [17]. The amount of mRNA available for translation is highly predicated on the survival of the newly synthesized strands. In the 3′ UTR, evolutionary conserved domains are present that correspond to elements in the mRNA that are highly prone to degradation by cytosolic ribonucleases [18]. Importantly, the instability of these mRNA elements is not absolute. In the setting of hypocalcemia, cytosolic *trans (*non-DNA mediated*)* activating factors may bind to the *cis* (DNA mediated)-acting instability elements and protect the mRNA from subsequent degradation [17]. Additionally, serum phosphate, independent of changes in the serum calcium, causes decreased binding of the cytosolic proteins [17, 19]. This results in deadenylation, de-capping, and subsequent degradation of the mRNA [18] (Fig. 4.3).

Translation and Protein Processing

PTH mRNA encodes a pre- (or signal) sequence of 25 amino acids and a basic pro-peptide of 6 amino acids [21]. PreProPTH (115 amino acids) is first synthesized on ribosomes that are bound to the membrane of the endoplasmic reticulum [6, 22]. As translation proceeds, the polypeptide, rich in hydrophobic residues, is transported into the endoplasmic reticulum where two amino (N)-terminal methionines (MET) are cleaved by methionyl amino peptidase ([23]). As the polypeptide chain is translocated across the ER, further proteolytic cleavage of the remaining signal sequence occurs at the glycyl-lysyl bond, resulting in 23 more amino acids being removed from the PTH precursor [6, 23]. The formation of ProPTH from preProPTH is estimated to occur in less than a minute [24].

ProPTH is exported in vesicles that bud from the transitional ER and carry their cargo through the ER-Golgi intermediate compartment and then to the Golgi network. Following entry into the *trans*-Golgi apparatus, the basic pro-peptide directs cleavage of the pro-sequence (6 amino acids) from the N-terminal to produce mature PTH (84 amino acids) ([25]). PTH is then packaged into either cytoplasmic (for storage) or secretory granules. The entire parathyroid biosynthetic process is estimated to occur in less than 1 h [26].

Regulated Secretion and Degradation of PTH and Its Derivatives

PTH secretion is regulated predominantly by calcium sensing receptors (CaSRs) located on the surface of chief cells [18] (Fig. 4.4). The CaSR is a seven-transmembrane G-protein-coupled receptor that is highly sensitive to changes in serum calcium [18]. For instance, a decrease of less than 1 mg/dL in serum calcium can cause PTH secretion to double [27] (Fig. 4.5). Sudden and sustained hypocalcemia results in elevations in PTH within 1 min, peaks at 4–10 mins, and then steadily declines to approximately 60 % of its maximum concentration, despite sustained hypocalcemia [18]. In contrast, the rate of PTH secretion is greatly suppressed when the serum calcium exceeds 9–10 mg/dL [27] (Fig. 4.5).

Following exocytosis from the chief cell, the liver and kidney metabolize PTH into amino (N)- and carboxy (C)-terminal fragments, which are ultimately cleared by glomerular filtration. Chief cells also partially degrade PTH (1–84) and secrete both N- and C-fragments directly into the circulation [6]. Traditionally, the N-terminal portion of PTH has been thought to constitute the

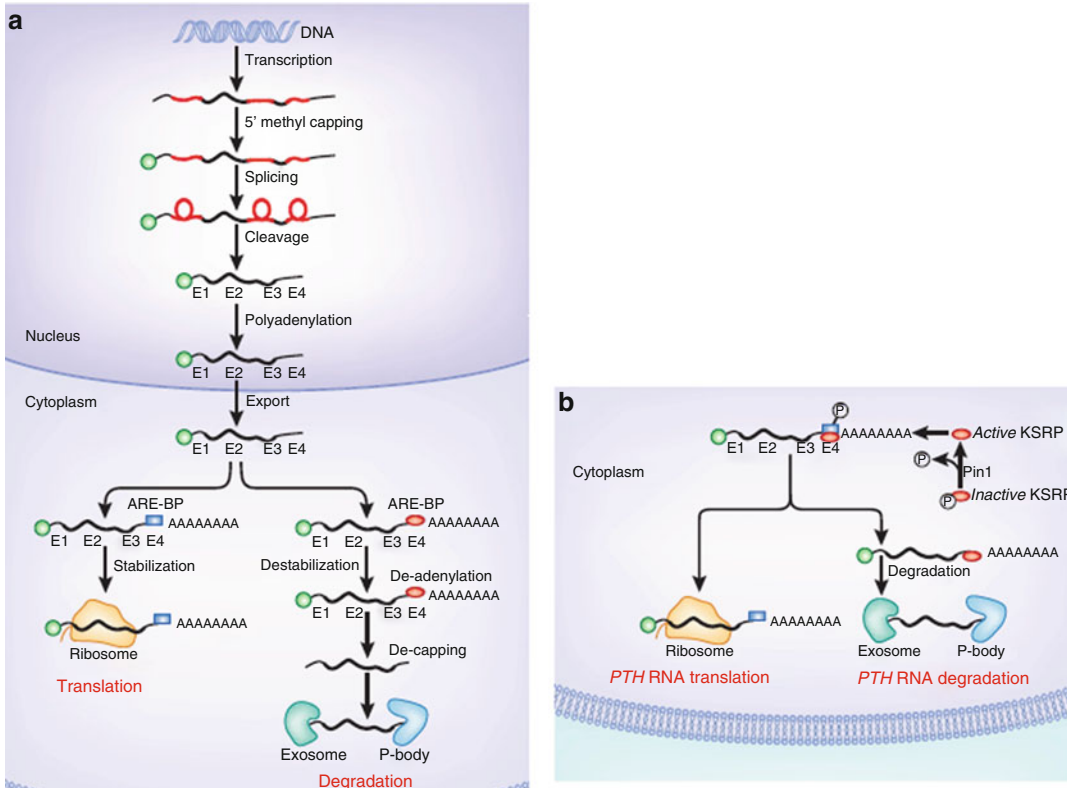

Fig. 4.2 (**a**) Cellular processing of mRNA. Nascent mRNA comprised of exons (E1 through E4) and intervening sequences (IVS) is processed in the nucleus by 5′-methyl capping, splicing, cleavage, and polyadenylation. In the cytoplasm, AU-rich element-binding proteins (ARE-BPs, blue box and red oval) bind to AREs within the 3′-region of RNA and stabilize or destabilize mRNA. Stabilized mRNA undergoes translation in ribosomes, whereas destabilized mRNA undergoes deadenylation, decapping, and degradation in exosomes or P-bodies. (Adapted from reference 130 with permission from the American Society for Clinical Investigation.) (**b**) Processing of mRNA-encoding *PTH*. Murine mRNA-encoding *PTH* is bound by ARE-PPs, which either stabilize or destabilize the mRNA. The ratio of activities of stabilizing/destabilizing ARE-binding proteins bound to mRNA-encoding *PTH* determines the half-life of the mRNA. KSRP is a mRNA-destabilizing ARE-BP for mRNA-encoding *PTH* that is active in its dephosphorylated state. The peptidyl-prolyl isomerase Pin 1 is responsible for the dephosphorylation of KSRP. In CKD, Pin 1 activity is reduced, and as a result less dephosphorylated (active) KSRP is available. Consequently, a stabilizing ARE-BP, AUF1, is active and mRNA-encoding *PTH* is degraded to a lesser extent, resulting in higher intracellular mRNA levels, more PTH synthesis, and secondary hyperparathyroidism. Abbreviation: P, phosphate. (Adapted from reference 130 with permission from the American Society for Clinical Investigation.) From: Kumar R, Thompson JR. The regulation of parathyroid hormone secretion and synthesis. J Am Soc Nephrol 2011; 22: 216–224

biologically active region [6]. Substitution or deletion of even one amino acid in the first N-terminal 34 amino acids significantly reduces the polypeptide's functional activity and potential to interact with the type 1 PTH receptor (PTH1-R) [6]. PTH fragments with conserved sequences in the first 34 amino acids [i.e., naturally occurring PTH (1–37), synthetic analogue PTH (1–34], PTHrP) are capable of mediating any number of activities that are classically associated with PTH [28].

The C-terminal of PTH (the last 50 amino acids) was previously thought to be biologically inert after translation [29]. Evidence now sug-

gests that C-PTH fragments interact with non-classical PTH receptors and exert biological effects that are independent and opposite to those of PTH (1–84) [30]. For instance, C-PTH fragments may bind to C-PTH receptors on osteoclasts and exert a direct antiresoptive effect on bone [31, 32]. A particular subset of C-PTH fragments, representing approximately 10 % of all C-PTH fragments, contains a partially preserved N-structure [33]. Compared to other C-PTH fragments, the N-truncated fragments, represented by the prototype PTH (7–84), may become increasingly important clinically because they have about a ten-fold greater affinity for the C-PTH receptor and inducing its antiresorptive effects [33]. Moreover, synthetic hPTH (7–84) has been shown to antagonize the calcemic effect of hPTH (1–84) and hPTH (1–34) in parathyroidectomized animal models, suggesting that the fragments may at least contribute to the PTH resistance commonly observed in the setting of renal failure [34, 35].

The relative concentrations of PTH (1–84) and C-PTH fragments are predominantly a reflection of the serum calcium and renal status of the patient. In the setting of normocalcemia and renal sufficiency, PTH (1–84) has a half-life

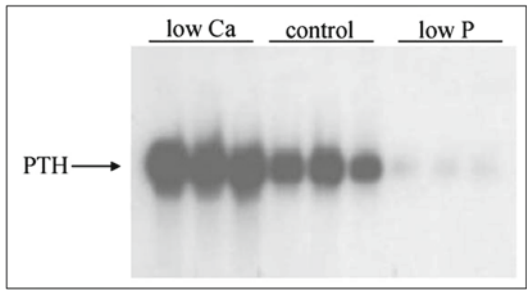

Fig. 4.3 Low dietary intake of calcium and phosphate decrease PTH mRNA levels. Weanling rats were fed control (0.6 % calcium, 03 % phosphate), low calcium (0.02 % calcium, 0.6 % phosphate) or low phosphate (0.6 % calcium, 0.02 % phosphate) diets for 14 days. Total RNA from thyro-parathyroid tissue from each rat was extracted and PTH mRNA levels determined by Northern blots. Each lane represents PTH mRNA from a single rat. From: Kilav R, Silver J, Naveh-Many T. Parathyroid hormone gene expression in hypophosphatemic rats. J Clin Invest 1995; 327–333 [20]

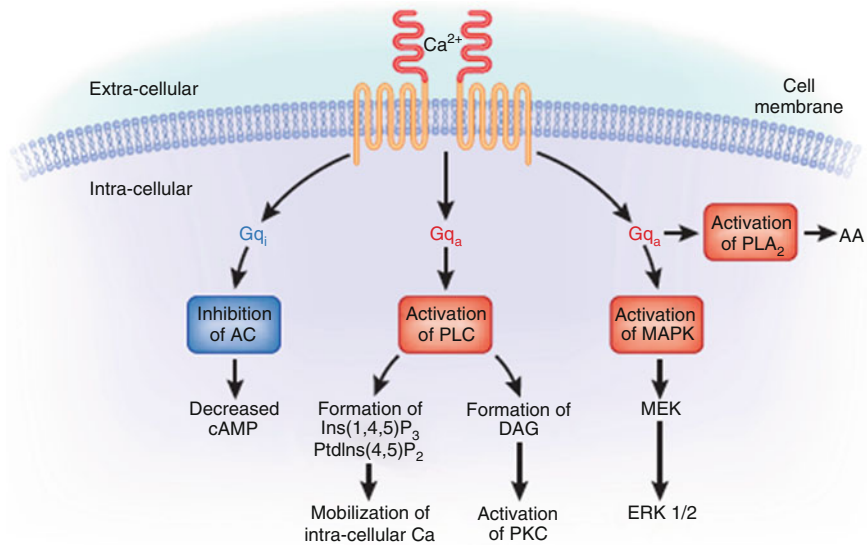

Fig. 4.4 Signaling pathway by which extracellular calcium (Ca2+) binds to the calcium sensing receptor (CaSR). Through the association of the CaSR with the i-type heterotrimeric G protein, $G_{i\alpha}$, adenylate cyclase (AC) activity is inhibited and cyclic AMP (cAMP) concentrations decrease. Association of the CaSR with the $G_{q\alpha}$ subunit of q-type heterotrimeric G protein results in the activation of PLC that increases inositol $(1,4,5)P_3$ and diacylglycerol (DAG) with attendant downstream effects, such as an increase in intracellular calcium that is mobilized from intracellular stores, and the activation of PKC. MAPK and PLA_2 are activated by $G_{q\alpha}$-dependent pathways with increases in MEK and ERK and an increase in arachidonic acid formation. From: Kumar R, Thompson JR. The regulation of parathyroid hormone secretion and synthesis. J Am Soc Nephrol 2011; 22: 216–224

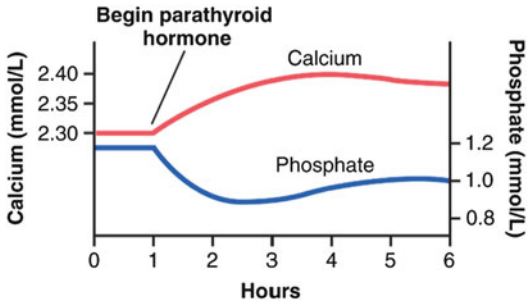

Fig. 4.5 Approximate effect of plasma calcium concentration on the plasma concentrations of parathyroid hormone and calcitonin. Note that chronic changes in calcium levels of only a few percentage points can cause as much as a 100 % change in parathyroid hormone concentration. From: Hall J. Parathyroid hormone, calcitonin, calcium and phosphate metabolism, vitamin D, bone and teeth, in Guyton and Hall textbook of medical physiology. Chapter 79. 11ed. Philadelphia: Saunders-Elsevier: 2011. Philadelphia 955–972

of 2–4 mins and accounts for approximately 20 % of total circulating PTH [36]. In patients with impaired renal clearance, the half-lives of PTH (1–84) and other PTH fragments with conserved sequences in the first 34 amino acids are mildly elevated and range from 4 to 6 mins [37]. In the setting of hypocalcemia and hypercalcemia, the relative concentration of PTH (1–84) compared with total circulating PTH ranges as high as 33 % or as low as 4 %, respectively [36, 26]).

In contrast to PTH (1–84), C-PTH fragments have an inherently longer half-life that ranges from 10 to 20 mins depending on the renal status of the patient [36]. C-PTH fragments account for approximately 80 % of circulating PTH in normal individuals and upwards of 95 % as glomerular filtration rate decreases [36, 26]). Similarly, the C-PTH fragments with partially preserved N-structure, such as PTH (7–84), act like other C-PTH fragments, and their concentration relative to PTH (1–84) increases in hypercalcemia and decreases in hypocalcemia [35]. In the setting of poor renal clearance, the N-truncated C-fragments accumulate and may account for up to 50 % (compared to only 15–20 % normally) of intact PTH (iPTH) immunoreactivity [34].

This at least partly explains why iPTH monitoring demonstrates a relatively slower decline following subtotal or total parathyroidectomy in the setting of chronic renal failure. Commercially available iPTH assays (first and second generations) for intraoperative iPTH monitoring lack specificity and overestimate the actual PTH (1–84) values because of cross-reactivity with PTH containing amino acids 7–84 (PTH 7–84) [37]. The artificially elevated iPTH levels may potentially hamper intraoperative evaluation of resection sufficiency leading to further surgical exploration that is otherwise unwarranted [37]. This problem of cross-reactivity with PTH (7–84) has prompted the development of a third generation of assays, which use antibodies targeted against an epitope containing the proximal 4–6 amino acids at the N-terminal [37]. While some authors propose that third-generation assays provide superior intraoperative data, it is not clear whether the implementation of these assays will translate into a reduction in failed parathyroid surgeries, decreased hypoparathyroidism, or decreased operating times [37]. It is unknown whether the clinical utility will ultimately exceed the longer incubation times and elevated costs associated with the newer assays.

Classical Actions of PTH

In general, continuous infusion of PTH causes calcium levels to rise until eventually reaching a plateau after about 4 h [27] (Figs. 4.6 and 4.7). In juxtaposition, the phosphate concentration declines relatively rapidly and reaches a plateau within 2 h [27]. This occurs because PTH increases the calcium and phosphate absorption from the bone and decreases the excretion of calcium by the kidneys. The PTH-induced decline in phosphate, then, is a consequence of the rapid excretion of phosphate, relative to the rate of phosphate reabsorption in bone [27].

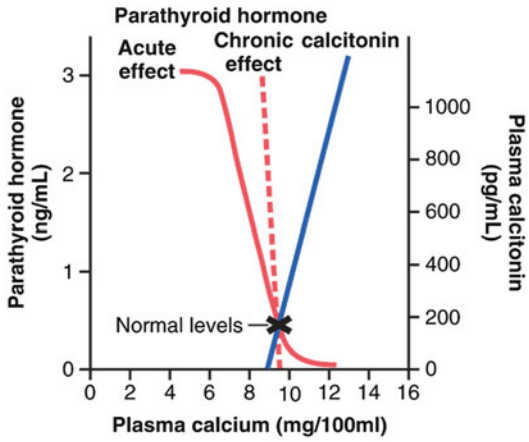

Fig. 4.6 Approximate changes in calcium concentrations during the first 5 h of parathyroid hormone infusion at a moderate rate. From: Hall J. Parathyroid hormone, calcitonin, calcium and phosphate metabolism, vitamin D, bone and teeth, in Guyton and Hall textbook of medical physiology. Chapter 79. 11ed. Philadelphia: Saunders-Elsevier: 2011. Philadelphia 955–972

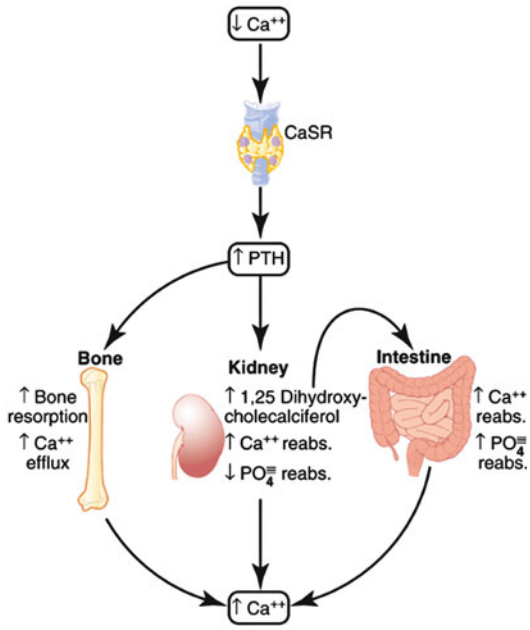

Fig. 4.7 Summary of parathyroid hormone (PTH) actions on bone, kidneys, and intestine in response to decreased extracellular calcium concentrations. *CaSR*, calcium-sensing receptor. From: Hall J. Parathyroid hormone, calcitonin, calcium and phosphate metabolism, vitamin D, bone and teeth, in Guyton and Hall textbook of medical physiology. Chapter 79. 11ed. Philadelphia: Saunders-Elsevier: 2011. Philadelphia 955–972

Bone

PTH acts on bone, containing upwards of 99 % of total body calcium stores, to release calcium in two stages [38]. The first phase, which occurs within minutes and rises steadily over hours, involves the release of calcium and phosphate stores from pre-existing bone cells. The bone is separated from the extracellular fluid by a membrane of interconnected osteoblasts and osteocytes referred to as the osteocytic membrane [27]. The osteocytic membrane contains a small amount of interim fluid, called bony fluid, whose calcium concentration is dictated by osteocytic pumps [26]. PTH binds to osteocyte receptors and increases the permeability of the bone fluid side of the osteocytic membrane, which causes the calcium concentration to increase in the bony fluid. The calcium ions that diffuse into the membrane cells from the bone fluid activate the calcium pump, which results in the rapid removal of calcium phosphate salts from the amorphous bone crystals that lie near the cells [27].

In the second phase, which occurs after several days or even weeks, PTH binds to osteocytes and indirectly induces the formation and proliferation of new osteoclasts [27]. The increased concentration of osteoclasts results in increased resorption of calcium phosphate salts from bone. The traditional view has been that osteoblasts, rather than osteoclasts, possess PTH receptors and activate second messenger signals through effects on RANKL and osteoprotegerin (OPG) [39]. As discussed previously, however, emerging evidence suggests that intact PTH (1–84), but not PTH (1–34), may bind directly to osteoclasts via C-terminal PTHRs [25].

Paradoxically, intermittent or pulsatile PTH administration stimulates bone formation relative to bone resorption. There is now level I evidence that daily or once-weekly subcutaneous injections of PTH (1–34) significantly increase bone mineral density at all skeletal sites except the radius and significantly reduces the risk of new fractures in postmenopausal women with prior fractures [40, 41]. It appears that PTH (1–34) improves bone collagen cross-link formation, microarchitecture, and bone mass, resulting in an overall

increase in bone strength [42]. The precise molecular mechanism by which this anabolic action occurs is not fully understood but likely occurs via the induction of particular target genes [43]. For example, when PTH binds to its associated receptor, the hormone induces a wave of RANKL expression that may induce either catabolic or anabolic processes depending on whether the PTH is given continuously or intermittently, respectively [44]. It is thought that the variable expression of RANKL in the osteoblasts may be related to varying levels of osteoclastogenesis [43]. Notably, both PTH (1–34) and PTH (1–84) have been shown to have equal potential in mediating anabolic bone formation, suggesting that the N-terminal interaction with the PTH1-R is relevant [45].

Kidney

In the kidney, PTH regulates the threshold for the excretion of calcium and phosphate. PTH1-Rs are predominantly located in the cortical thick ascending limb loop of Henle and the distal convoluted tubules of the nephron [27]. In the setting of hypocalcemia, PTH binds to PTH1-Rs on the tubule segments and stimulates active transport of Ca^{2+} preventing excessive urinary excretion. In the setting of hypercalcemia, calcium binds to CaSRs with a subsequent increase in calciuresis. PTH is also the predominant regulator of phosphate reabsorption and excretion in the nephron. The majority of renal phosphate reabsorption occurs in the proximal tubules via type IIa Na-P_i cotransporter [46]. In the setting of elevated serum phosphate, PTH internalizes and degrades the apical Na-P_i and rapidly increases the phosphate excretion [46]. Calcitriol likely plays an important role in the regulation of these cotransporters [46].

Ingested ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3), which may also be synthesized from sunlight, are converted to 25-hydroxyergocalciferol (25-hydroxyvitamin D_2) and calcidiol (25-hydroxyvitamin D_3) in the liver. Following their release into the circulation, these two hepatic metabolites may be measured from the serum to determine a patient's vitamin D status. In the proximal tubules, a portion of circulating calcidiol is converted to calcitriol. Calcitriol increases both calcium and phosphate absorption from the gastrointestinal tract. Circulating PTH acts at the proximal tubules and governs the amount of calcidiol that is converted to calcitriol and indirectly regulates the rate of calcium and phosphate absorption from the intestine [38] (Fig. 4.8). When serum calcium is below approximately 9 mg/dL, PTH enhances the enzymatic activity of alpha-1-hydroxylase in the proximal tubules resulting in the synthesis of calcitriol [47]. At elevated calcium levels, PTH secretion is suppressed and calcidiol is instead converted to $24,25(OH)_2D_3$, which has less than 1/1,000 of an effect on increasing intestinal calcium and phosphate absorption [27]. The PTH-induced conversion to active vitamin D metabolite explains why approximately 50 % of patients with primary hyperparathyroidism may present with normal or elevated levels of calcitriol in spite of a 40 % prevalence of vitamin D deficiency.

As kidney function declines, parathyroid function is stimulated by (1) insufficient production of calcitriol by the kidney, (2) calcium deficiency, and (3) elevated phosphate levels [48]. In the early stages of chronic kidney disease (CKD) (GFR > 60 ml/min/1.73 m^2), dietary phosphorous intake initially suppresses calcitriol production, which subsequently induces PTH secretion and prevents the development of hyperphosphatemia [49]. As CKD progresses (GFR < 30 ml/min/1.73 m^2 of body surface), however, phosphorous levels escalate and induce hypocalcemia [49]. As discussed previously, elevated serum phosphate and low serum calcium both increase PTH secretion. Prolonged and excessive levels of PTH cause high turnover bone disease and may cause other effects that are not classically associated with the hormone: glucose intolerance, polyneuropathy, dyslipidemia, cardiac hypertrophy and dysfunction, and uremic inflammation [49]. Several studies have investigated the role of elevated PTH as a nonspecific uremic toxin. It is important to remember, however, that a complex relationship exists between elevated PTH and other potential factors involved in mineral metabolism in CKD, and thus the role of PTH as an

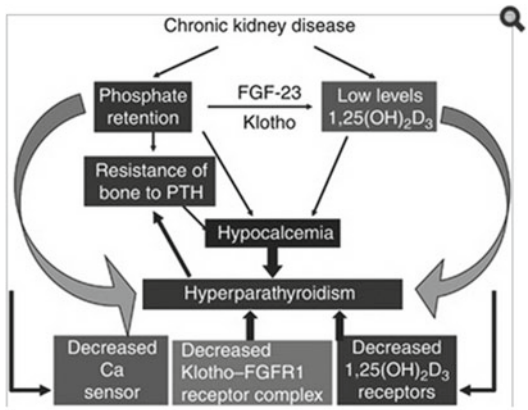

Fig. 4.8 Summary of the factors involved in the pathogenesis of secondary hyperparathyroidism. A decrease in ionizing calcium is crucial in the development of secondary hyperparathyroidism. Changes in ionized calcium are secondary to phosphate retention and low levels of $1,25(OH)_2D_3$. Phosphate retention increases fibroblast growth factor (FGF)-23, which, in conjunction with its cofactor, the Klotho protein decreases the activity of the 1 α-hydroxylase and increases the 24α-hydroxylase, thus decreasing the levels of circulating $1,25(OH)_2D_3$. In addition, phosphate retention, independent of changes in ionized calcium, increases the synthesis of parathyroid hormone (PTH). $1,25(OH)_2D_3$, independent of calcium, suppress the transcription of the *PTH* gene. Decreases in the vitamin D receptor, calcium sensor receptor, and Klotho-FGFRI receptor complex in the parathyroid gland also aggravate the development of secondary hyperparathyroidism. From: Slatopolsky E. The intact nephron hypothesis: the concept and its implications for phosphate management in CKD-related mineral and bone disorder. Kidney Int Suppl 2011; 79(S121): S3–S8

independent risk factor for uremia-related complications is not entirely clear [49].

In any case, uremic hyperparathyroidism (UHPT) is a relatively common complication occurring in patients on hemodialysis and likely contributes to the development and progression of chronic kidney disease-mineral bone disorder (CKD-MBD) [50] (Fig. 4.8). Patients with UHPT have an increased risk of all-cause and cardiovascular mortality, which has been linked to an accelerated rate of atherosclerosis and arterial calcification [50]. Thus, the prevention and control of UHPT are critical in dialysis patients as the excessive PTH and/or other uremic factors exert toxic systemic effects. At present, the major principle guiding treatment of UHPT is tight calcium and phosphorous control. While higher doses of vitamin D therapy, acting through the activation of VDR, have demonstrated efficacy in reducing hyperparathyroidism and increasing survival, the use of high-dose vitamin D has been associated with exacerbating hyperphosphatemia and causing hypercalcemia, potentially increasing the risk of atherosclerosis and arterial calcification [51, 52]. Cinacalcet has been shown to effectively lower serum iPTH, calcium, and phosphorous levels and may even provide cardiovascular protection in patients on hemodialysis [53, 54]. Cinacalcet allosterically enhances sensitivity to CaSR and also increases the expression of VDR in the parathyroid gland [50]. Moreover, the concurrent use of cinacalcet and low-dose vitamin D may increase the efficacy in treating UHPT without the elevated cardiovascular risk associated with high-dose vitamin D therapy [50]. In any case, these concepts illustrate how our evolving knowledge regarding PTH, calcium, phosphate, and vitamin D feedback mechanisms is key in the management of parathyroid-related disorders.

Summary

The biological pathway of PTH has been described from gene expression to PTH intracellular signaling. Physiologic fluctuations in plasma calcium are dependent on the proper manufacturing, secretion, and degradation of PTH. The classical actions of PTH are well known. In bone, PTH may act as a catabolic or anabolic agent depending on whether the administered PTH is continuous or pulsatile, respectively. In the distal tubular cells of the kidney, PTH directly regulates the amount of calcium excreted in the urine. In the proximal tubular cells, PTH regulates the conversion of vitamin D to its active metabolite calcitriol, which increases the amount of calcium and phosphate that is absorbed from the intestine. Finally, different circulating PTH fragments have been identified that are independent and antagonistic to the classical downstream actions of PTH (1–84). Future research is required to determine both the physi-

ological and pathological implications associated with non-classical PTH molecular signaling.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion

A fundamental understanding of parathyroid physiology is crucial for both the treating physician and surgeon to master. For the physician, this understanding will be employed in diagnosis of hyperparathyroidism and the postoperative management of its sequelae. For the surgeon, this understanding is essential for confirming a diagnosis requiring surgery and assessing the response of the disease to surgical intervention.

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Part III

Parathyroid Diseases

Single-Gland Primary Hyperparathyroidism: Classic and Early Disease

5

Dana L. Madison

Contents

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Introduction

Primary hyperparathyroidism (PHPT) is hypercalcemia caused by inappropriate Parathyroid Hormone (PTH) secretion from one or more of the four parathyroid glands. The typical presentation is an asymptomatic PTH-dependent hypercalcemia from a single-gland adenoma, with varied risks for kidney stones and declining bone mass. Subtleties and nuances exist in diagnosing PHPT; including, patients in whom there is minimally elevated to high normal plasma calcium levels, variable urine calcium levels, absence of significant target organ effects, vague and non-specific symptoms, ectopic parathyroid glands, syndromic Hyperparathyroidism, and the PHPT mimicking disorder Familial Hypocalciuric Hypercalcemia (FHH). Other Chapters in this text will address these issues in significant depth. This Chapter will present an overview of both the more severe, classical Primary Hyperparathyroidism and the current, most common (classic) presentation of PTH-dependent hypercalcemia, single-gland Primary Hyperparathyroidism; focusing on elements of presentation, diagnosis and differential diagnosis, and treatment.

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Clinical Presentation and History

Primary Hyperparathyroidism most commonly is an asymptomatic hypercalcemia due to autonomous production of PTH from a single parathyroid adenoma (85 % prevalence; [1]) with variable effects on two primary target organs, the skeleton and kidney.

PHPT has a "classical" presentation that historically had more severe, widespread symptoms and significant target organ involvement. The current "classic" presentation of PHPT is predominately asymptomatic with less skeletal and renal involvement. Both of these clinical presentations commonly occur from a single-gland adenoma. Examining the differences between the two is important for determining both the population and individual risk factors in disease progression, organ involvement, and impact on mortality in surgical and nonsurgical patients.

The Evolution of the Classical Presentation to the Current, Asymptomatic PHPT

PHPT occurs predominately in women (3:1 versus male) age >50 years and the disease severity shows geographic variability. For example: In the United States (US) the incidence is relatively stable to slightly declining, depending on the database used, although in some racial groups there has been increasing prevalence (ranges: all women 34–268 per 100,000 patient years and all men 13–85 per 100,000 patient years) [2, 3]. In contrast, other geographic centers still report a significant frequency of more severe, classical disease. In Asia, the evolving access to medical care reveals a shift towards the newer "classic" asymptomatic presentation; likely representing increased access to testing. The prevalence of asymptomatic PHPT rose from 5 to 59 % in Hong Kong between 1973 and 2002 [4] in contrast to a mainland Chinese cohort examined between 1958 and 1993 where 97 % of patients had target organ effects including nephrolithiasis, osteoporosis, pathologic fractures, and severe skeletal changes such as osteitis fibrosa cystic [5, 6]. A separate Chinese cohort had an increased incidence of the asymptomatic presentation from 20 to 60 % between 2000 and 2010 whereas previously about 60 % of patients had the classical form. Additionally, recent cohort data from Brazil and Argentina also showed more classical, symptomatic disease (53 % of all PHPT diagnoses; 25 % nephrolithiasis, 25 % osteitis) with very low bone mineral density and single-gland presentation in 87 % of PHPT patients [7–9]. In a cross-sectional study comparing data from Italy and the US, Italian men and to a lesser degree women, had greater serum calcium levels and lower bone density despite having similar PTH levels with a matched US cohort [10]. These geographic studies highlight PHPT progression, suggesting that time of disease activity, access to medical evaluation, and possibly other regional variables including genetic and dietary differences will influence the degree of pathology. Whether there should be adjustment to the treatment guidelines to reflect regional differences is not yet clear. Further monitoring is needed to determine if there will be a continued shift away from the classical phenotype towards the asymptomatic phenotype in these geographic centers as there has been in North America and in parts of Europe.

The asymptomatic PHPT common to North America and Europe is characterized by nonspecific symptoms familiar to any primary care patient population. The list of mild symptoms potentially attributable to hypercalcemia from PHPT may include fatigue, neuromuscular complaints, polydipsia, and polyuria. More significant neuromuscular symptoms can be seen with severe hypercalcemia, although the severity of the hypercalcemia may not correlate directly with disease severity. Some surveys note a constellation of neuropsychiatric and constitutional complaints, but these are not often reversed following surgery [11, 12], suggesting that these common symptoms should not be over-stated as the result of PHPT. The primary target organ effects are in the kidney as nephrolithiasis or nephrocalcinosis, and the skeleton as preferential cortical bone loss at the distal 1/3 radius. Severe skeletal changes are infrequent in Europe and

North America (<5 %) where nephrolithiasis has also declined in all PHPT patients from 30 % (before 1970) to 10–20 %. Conversely, it is estimated that 3 % of all kidney stone patients have PHPT [12, 13]. More frequent lab testing likely has decreased the length of time to diagnosis and subsequently the incidence of severe skeletal sequelae and nephrolithiasis. In contrast, it is still common to see minimal hypercalcemia not evaluated in patients until years after the initial abnormality was first found. Time of disease presence is likely one variable in disease progression at the target organs and potentially for symptoms. Very mild hypercalcemia may escape notice longer and therefore not trigger an evaluation when compared with more severe hypercalcemia. In the classical presentation and possibly in mild PHPT present for years, there may be more significant neuromuscular symptoms including progressive fatigue, weakness, or even myopathy [14]. There also may be an increased frequency of neuropsychiatric and gastrointestinal symptoms, specifically, common gastritis or gastroesophageal reflux complaints, depression, anxiety, and mild cognitive changes [15]. Peptic ulcer disease is not significantly increased and pancreatitis is seen only rarely with severe hypercalcemia. These observations suggest that all patients with PHPT require a complete evaluation for target organ involvement. The prevalence of the classical presentation in other geographic centers or in patients having PHPT for many years highlights that PHPT has the potential to cause severe clinical harm when left undiagnosed, requiring prompt evaluation of any hypercalcemia. Whether there are specific risk factors predisposing patients to increased disease severity or more rapid progression is unknown.

Considerations for PHPT Effects on Mortality

Some studies have suggested an increased risk of mortality and morbidity in severe classical PHPT [16, 17]. Cardiovascular changes may occur, including arterial and valvular calcifications with increases in all cause cardiovascular mortality. These long-term risks are likely significant enough to warrant consideration in at-risk populations where PHPT has been present for many years although the definition of that threshold is not clear; however, the risks in asymptomatic PHPT are also not at all clear and lack prospective trials. Most outcomes studies failed to show direct benefit to surgery versus observation in cardiac functional or structural indices [18, 19], despite data suggesting that PTH elevations and/or hypercalcemia may be associated with worsening of Left Ventricular hypertrophy, aortic valve calcification, and carotid intimal medial thickness [20, 21]. Variability in these observational studies and the lack of controlled prospective trials suggest that progression of cardiac disease in asymptomatic PHPT should not prompt either additional evaluation of these risks nor their inclusion in surgical criteria. Current clinical guidelines do not recommend cardiovascular risk factor measurements as part of the diagnostic evaluation or surgical intervention solely for reduction in cardiovascular sequelae [12, 22].

If an increase in all cause mortality exists in classical disease, is there also a risk in patients with long-present, untreated asymptomatic disease and are there criteria for including these factors in the clinical decision-making algorithm? This premise is critical to our understanding of the differences between these two patient populations and by extrapolation, the outcomes in surgically and nonsurgically treated patients. Variability in data collection, the at-risk study populations, definitions of diagnosis, and variable mortality of up to 30 % in some cohorts have confounded interpretation, but analyses suggest there is a significant mortality risk in some patients [17, 23]. A recent study of an Australian cohort showed a significant decreased 10-year survival of all PHPT patients compared with the control population (versus no PHPT; relative survival rate 87 %), while there was no statistical difference in survival between the surgical and nonsurgical PHPT groups [24]. Further comparison of the PHPT groups (surgically and nonsurgically treated, compared to controls) revealed a slow decline in relative nonsurgical patient survival through 12 years from diagnosis, followed by a more rapid decline in years 12–20 (63 %, 20-year relative

survival) that was independent of calcium and PTH levels. This is similar to some studies where there was no mortality difference with short-term follow-up in the treated versus untreated PHPT groups, or others where nonsurgically treated PHPT patients had increased all-cause mortality with variable conclusions on whether a positive correlation of PTH and calcium was present [17, 23, 25, 26]. Other study populations have suggested that serum PTH levels independent of serum 25-hydroxy Vitamin D3 (25(OH)D3) and calcium levels may contribute to increased mortality, although the mechanism for this association is not clear [27, 28]. These variable mortality data require further investigation to answer three important questions:

1. Does PTH-dependent hypercalcemia from PHPT result in a time-dependent increase in mortality and if so,
2. Does surgical correction before a certain time and/or disease severity threshold reduce the all-cause mortality, and
3. Is there a specific marker or set of risk factors that will define these at-risk patients?

Until these issues are resolved in randomized, well-matched populations with controls, the question of direct impact of PHPT on mortality remains open.

Consideration for surgical management in at-risk populations with single-gland disease who do not yet meet surgical criteria is a reasonable question, especially since well-defined skeletal and renal sequelae can be improved. Long-term studies and prospective age-matched cohorts are needed to replicate the Australian cohort [24], since these and other longitudinal data [29] suggest that observation past a threshold of years results in a transition of mortality and morbidity to levels associated with classical disease and with significant worsening of all cause mortality. Further analysis of at-risk matched populations of surgically treated and medically observed patients are required to determine if there is a temporal or clinical marker threshold independent of current surgical criteria where surgery may be offered to all appropriate patients.

Diagnosis and Differential Diagnosis

Ongoing efforts to define the presentation, progression, and therapeutic management of asymptomatic PHPT lead to the 2009 and 2014 NIH Consensus Conference guidelines for evaluation and management [30, 31]. The most recent iteration extensively covers the presentation, diagnosis, medical and surgical management of PHPT and these are reviewed specifically in other Chapters of this text. The basis for many of these guidelines is PTH-dependent hypercalcemia from asymptomatic, single-gland PHPT, the predominate form in North America and Europe. These patients constitute the bulk of outpatient evaluations for hypercalcemia.

The Biochemical Diagnosis of PHPT

The typical PHPT patient has mild hypercalcemia, usually less than 1 standard deviation (approximately ≤1.0 mg/dL; 0.25 mmol/L) above the upper normal range limit of serum calcium. Hypercalcemia is usually found on incidental lab screening since these asymptomatic patients rarely have specific physical complaints that would suggest a calcium abnormality. The evaluation focuses first on biochemical confirmation of the diagnosis, then target organ involvement and finally the need for either medical or surgical intervention or both, with diagnostic imaging only becoming necessary if surgical correction is pursued.

The biochemical definition of PHPT includes: hypercalcemia, hypophosphatemia, a low to low normal 25(OH)D3 level, a normal to increased 1,25-dihydoxy Vitamin D3 [1,25$(OH)_2$D3] level, elevated PTH, and variable 24-h urine calcium levels that are frequently high normal to overt hypercalciuria in ~30 % of patients. Patients with severe hypercalciuria (>400 mg/24 h) may benefit from kidney stone risk analysis using metabolic urine profiles [30, 32]. Renal function is usually normal, but a reduction in overall Glomerular Filtration Rate (GFR) and a rise in serum creatinine can occur in those patients with baseline renal dysfunction or when using GFR

altering medications such as diuretics. The thiazide diuretics may exacerbate hypercalcemia in older patients or in those using calcium supplements. Thiazides can also unmask very mild PHPT in the setting of Vitamin D3 deficiency when hypercalcemia is not evident prior to thiazide initiation.

Plasma calcium levels are usually tightly bracketed within a sub-fraction of the usual laboratory range; therefore, all elevated plasma calcium levels should be viewed as abnormal and investigated. Even high normal calcium levels might be considered suspicious in some patients as concomitant Vitamin D3 and/or dietary calcium deficiency or significant hypercalciuria may blunt the hypercalcemic effect of PHPT resulting in calcium levels just below the abnormal range (e.g., 9.9–10.3 mg/dL, when the lower abnormal limit is 10.4 mg/dL). These levels may be appropriate for a small fraction of the population with normal renal function, but careful examination of other deficiencies often increases the suspicion for mild PHPT. Upwards of 90 % of all confirmed outpatient hypercalcemia is due to PHPT or Humoral Hypercalcemia of Malignancy. If the hypercalcemia is determined to be PTH-dependent then the majority of these patients will have PHPT from a single-gland adenoma, with a small subset (~10 %) having multiple gland hyperplasia, Familial HPT, Syndromic PHPT (Multiple Endocrine Neoplasia (MEN) 1 or 2) or FHH.

Two Significant Confounders in the Differential Diagnosis of PHPT

Most outpatient hypercalcemia is likely due to PHPT; however, one must consider FHH and the issue of normocalcemic hyperparathyroidism in PHPT differential diagnosis and prior to determining who is an appropriate surgical candidate.

The true incidence of FHH is not well understood. Differentiation of PHTP from FHH is critical since some case series estimate between 10 and 24 % of all failed parathyroidectomies may be due to misdiagnosis in a patient with FHH, suggesting the overall incidence of FHH may approach 1 in 10^3–10^5 [33, 34]. The most recent (2014) PHPT diagnosis guidelines have reinstituted the recommendation for measuring 24-h urine calcium and calculating a calcium/creatinine ratio (Ca/Cr) in all suspected PHPT patients. In those who do not meet the classic definition of biochemical hyperparathyroidism, further workup including repeating the Ca/Cr, correcting calcium or Vitamin D3 deficiencies, adjusting renal acting medications and genetic testing (CaSR; Calcium Sensing Receptor) in appropriate patients is necessary to find FHH patients who might otherwise have an unneeded surgery [30, 35]. Interestingly, there is small subset of FHH patients that have demonstrable adenomas. Whether these patients are at greater risk for bone density loss or nephrolithiasis is not clear. In both these FHH patients and those with primary hypercalciuria, there are likely physiologic influences via the CaSR that may induce parathyroid hyperplasia, so adenoma development and even multigland involvement in these patients further confounds the diagnostic overlap with PHPT. Additional case series and extended follow-up are required to examine any mutation-/genotype-specific risk in these and all FHH patients. There are no current prospective matched cohort studies or guidelines addressing these overlap patients, so careful and coordinated individual assessment is warranted to determine the appropriate risks and benefits for either medical or surgical intervention. Surgical therapy is not required in a patient with biochemically and/or genetically proven classic FHH.

Another recent confounder to PHPT differential diagnosis is a patient with an upper normal serum calcium level and elevated PTH that has been termed "normocalcemic hyperparathyroidism." The PTH elevation in a number of these patients is appropriate and may be related to secondary causes such as Vitamin D3 deficiency, medications (e.g., lithium), primary hypercalciuria, or renal failure and therefore does not require an evaluation for PHPT or surgical intervention. As previously suggested (above), some of these patients will have very mild PHPT and are Vitamin D3 and/or calcium deficient and will manifest hypercalcemia if adequate stores are

replenished and the patient follows a normal calcium diet. Once these confounders are ruled out there may still be a very small subset of all patients with PTH elevations and an inappropriate PTH response to calcium (prevalence estimated as 0.4–3.1 %; [36]). Some of these patients will proceed toward overt hypercalcemia within 3 years [37] and therefore have PHPT. Proper interpretation of laboratory data is necessary to correctly rule in or out the appropriate diagnosis so only PHPT patients that will benefit from surgical intervention are offered a surgical approach.

Clinical Manifestations

In Primary hyperparathyroidism the two primary target organs are the skeleton and kidney.

Classical PHPT leads to significant skeletal changes including demineralization, bone cysts, brown tumors, and subperiosteal reabsorption. The skeletal manifestations in milder, asymptomatic PHPT are confined to an increased risk of bone loss and a long-term potential increased risk of fracture from bone quality changes.

Skeletal Effects

Bone loss in PHPT is most prevalent at cortical bone of the distal 1/3 radius, whereas trabecular bone at the hip and spine is more preserved. Bone turnover accelerates in PHPT and bone biopsies show a reduction in micro-architectural stability [38, 39], which can increase overall fracture risk. Occasionally accelerated bone loss similar to that of post-menopausal osteoporosis is seen; therefore, a complete bone loss risk evaluation should be completed on each PHPT patient. Measurement of cortical bone density by DXA (Dual energy X-ray Absorptiometry) is a critical component for quantitation of target organ risk from PHPT. Despite recommendations in 2009 for 3-site Bone Mineral Density (BMD) measurements in all PHPT patients [31], these are not routinely performed in preoperative assessments [40]. Disparate 3-site BMD with preferential low bone mass or osteoporosis at the distal 1/3 radius compared to the hip and spine can be a clue in the patient with minimal or intermittent hypercalcemia that PHPT has been present longer than suspected and also serves as a marker for clinical intervention if there is significant bone loss or osteoporosis. Other studies using newer bone density or bone quality measurements demonstrate that trabecular bone (hip, spine) is likely affected even in mild disease, suggesting a more global skeletal affect and increased risk of bone loss and fracture at all sites.

Increased rates of bone loss and osteoporosis are associated with an increased rate of fracture; however, in PHPT a direct association with increased fracture rates is not clear. Most cohort studies contain mixed populations of asymptomatic and more severe, classical disease where fracture risk is increased [41, 42]. There are differences in some studies for vertebral and nonvertebral fracture risk with some reporting no risk and some an increased risk for both vertebral and nonvertebral sites, especially the distal 1/3 radius [43, 44]. Metabolic factors including low Vitamin D3 levels may independently contribute to fracture risk in these cohorts, irrespective of PTH levels [45]. Despite the limited data and mixed populations of those PHPT patients with asymptomatic versus classical disease, there appears to be an overall increased risk of fracture in PHPT. Other factors leading to bone loss in men or pre-menopausal women, active post-menopausal bone loss, or significantly low bone mass (t-score <−2.0) at more than one site especially in younger patients (age <50 years old) are important additive risks for bone loss and fracture when present with PHPT. More advanced spine or hip bone mineral density loss found in a newly diagnosed PHPT patient may confer an increased fracture risk. If future data in nonsurgical PHPT patients further characterizes an increased hip or lumbar spine fracture risk and/or an increase in overall mortality and morbidity, this would suggest a reexamination of the bone density and bone loss criteria used for recommending surgery. How the time of disease, metabolic factors, and other risk factors for bone loss affect the overall fracture incidence and risk of future fracture in nonsurgically treated patients are important questions to be answered in well-matched prospective trials.

Renal Effects

The effects of PHPT on the kidney are both metabolic and pathologic. Nephrolithiasis and nephrocalcinosis are still relatively common even in asymptomatic PHPT. Clinically silent stones in PHPT patients are estimated at 7–15 % when screening abdominal ultrasound or spiral CT is performed [46] and at 55 % in mixed symptomatic/asymptomatic populations [47]. PHPT increases the filtered load of calcium and eventually can lead to absorptive hypercalciuria, one risk factor for stone development. Additionally, the elevated PTH increases renal production of $1,25(OH)_2D3$ by conversion from 25(OH)D3 through direct activation of 1-alpha hydroxylase, increasing calcium absorption from the intestine. Chronic hypercalciuria may lead to reduction in GFR and acceleration of age related renal decline or failure. Other metabolic and genetic risk factors in stone development suggest that for most patients with nephrolithiasis, hypercalciuria is not the sole risk factor. A more comprehensive stone risk analysis is now recommended with overt hypercalciuria (>400 mg/24 h) or in those PHPT patients with documented nephrolithiasis/nephrocalcinosis [30]. These 24-h urine panels assess a variety of risk factors (e.g., oxalate) that increase the risk of stones in the setting of hypercalciuria and aid in prescribing appropriate therapeutic interventions including increased hydration, low oxalate diets or decreasing urine acidity with potassium citrate.

Summary: Differential Diagnosis and Clinical Manifestations

Patients with asymptomatic hypercalcemia presumed to have single-gland PHPT should have a complete clinical workup to establish the biochemical diagnosis and assess their risks for complications. Once the diagnosis of a PTH-dependent hypercalcemia is made, differentiating single-gland PHPT from multigland or syndromic PHPT requires a thorough assessment of presentation, family history, and appropriate imaging studies. Careful evaluation of patients in whom minimal calcium elevation and/or low to low normal urinary calcium levels are found is required to resolve overlap with FHH, avoiding mis-diagnosis and unnecessary surgery.

A workup for hypercalcemia in the asymptomatic patient includes:

1. A clinical assessment for the extent and length of hypercalcemia and any family history of hypercalcemia, personal or family history of parathyroid surgery, kidney stones and metabolic bone disease, ruling out secondary causes of PTH elevations or non-PHPT causes of hypercalcemia,
2. A metabolic workup:
   (a) Laboratory assessment [serum total and ionized calcium, albumin, phosphorous, magnesium, PTH, 25(OH)D3, alkaline phosphatase, creatinine, urine calcium and creatinine with calculated Ca/Cr] and,
   (b) Evaluation of stone history, risk factors and where indicated complete stone risk analysis with a biochemical 24-h urine panel including calcium, oxalate, pH etc.
3. A clinical assessment for the sequelae of PHPT:
   (a) A 3-site DXA scan encompassing the distal 1/3 radius, hip, and spine with risk factor analysis for bone loss and fractures and,
   (b) Diagnostic imaging studies for the kidneys (stones) and skeleton (fractures) where appropriate.
4. Diagnostic imaging to guide the surgical management is performed in those patients deemed to have PHPT, meet surgical criteria and are candidates for surgical correction. This also aids in the differentiation of single versus multiglandular disease that changes the surgical approach and management. Sensitivity and site-specific preference often guide imaging choices and ultrasound, nuclear Sestamibi subtraction scans, and 4-dimensional CT all have their appropriate roles. Many centers now choose high-resolution ultrasound as their initial method.
5. Medical management of bone loss and fracture risks, stone formation, and long-term hypercalciuria risks if present should be pursued in nonsurgical patients.

6. Further clinical assessment in appropriate patients for those suspected of having either multigland disease including syndromic HPT (Familial PHPT or risks of MEN) or FHH prior to surgery. These include those patients in whom the clinical or biochemical presentation does not fit the typical paradigm for single gland, asymptomatic classic PHPT.

Management and Treatment of PHPT

PHPT is treated either through surgical correction in the appropriate patient, or long-term medical management and observation. Surgical removal of an adenoma is the only curative therapy for single-gland PHPT. Medical management strives to minimize complications from hypercalcemia, skeletal and renal effects. Surgical cure of hyperparathyroidism normalizes serum calcium, reduces the risk of nephrolithiasis and significantly improves bone density.

For patients with severe hypercalcemia, hypercalcemic crisis, presentation of the "classical" form of PHPT with significant pathologic sequelae or even with more overt mild disease with nephrolithiasis or osteoporosis, there is clear consensus and indication for surgery.

For asymptomatic hypercalcemia patients with or without single-gland hyperparathyroidism; recommended indications for surgery [30], preoperative, operative and postoperative management [1], medical management of the clinical complications or long-term medical management [22] and decision points for reconsidering surgery in a patient who has been medically managed [30] were recently re-examined and consensus statements issued. The workup and management of these patients is a critical cooperative point between surgical and medical physicians to provide these patients with complete and current opinions on their short- and long-term care.

Current Surgical Criteria

The 2015 recommendations for surgery include:

1. A Bone Density *t*-score < −2.5 at any of the three sites.
2. A vertebral fracture or any fragility fracture.
3. A 24-h urine calcium >400 mg/24 h and increased stone risk by biochemical profile.
4. The radiographic presence of nephrolithiasis or nephrocalcinosis.
5. Age <50 years old.
6. Serum calcium persistently 1 mg/dL (0.25 mmol/L) above the upper limit of normal.
7. A creatinine clearance <60 mL/min.

In patients undergoing medical therapy or monitoring, significant changes in any of the above criteria can be an indication for surgery:

1. If monitored calcium levels become persistently >1 mg/dL (0.25 mmol/L) above the upper normal range,
2. If there is worsening real function (decline in GFR <60 mL/min),
3. If there is a new kidney stone,
4. If there is a new vertebral or fragility fracture, or
5. If there is a statistically significant decline in the BMD by DXA measurement or the bone density declines into the osteoporotic range. Additionally, consideration for surgery can be made when the BMD is between −2.0 and −2.5 and significant fracture risks are present and/or a significant decline in BMD has occurred.

Low Bone Mass and Fracture Risks as Surgical Indications

Multiple longitudinal studies comparing Parathyroidectomy and observation have noted significant BMD increases in both male/pre-menopausal female patients or post-menopausal

women within 1–8 years of surgery, with the greatest increases at the Lumbar spine and femoral neck while variable gains are noted at the distal 1/3 radius [16, 48, 49]. In one cohort, bone density improved 8.2 % (Lumbar spine), 12.7 % (Femoral neck) and 4 % (Radius) after 4 years, except in post-menopausal women who gained 12.5 % at the Lumbar spine. Further analysis in a similar cohort showed rapid increases after one year (Lumbar spine, 8 %; Femoral neck, 6 %; Radius, not significant) and sustained increases at a lower rate through 10 years (Lumbar spine 12 %, Femoral neck, 14 %) [50, 51]. Other groups have noted similar gains in genetically different cohorts. A Japanese study reported a significant 15 % increase at the Lumbar spine and 23 % gain at the distal 1/3 radius in male and pre-menopausal female patients, with similar numbers in post-menopausal women [52]. Data on fracture risk reduction are limited but suggest decreased lumbar spine fractures over 5 years of follow-up in surgically treated patients [53]. One would predict that removing the negative influence of chronic PTH elevation on bone remodeling would increase bone formation and decrease the long-term fracture risk if other bone loss risks were also adequately managed. These data suggest that surgery also should be considered in patients with initial lower Lumbar spine bone mass, inclusive of pre-menopausal women or men with t-scores in the significant low bone mass range (*t*-score ≤2.0), since these patients have less than age predicted median bone mass and therefore increased fracture risk when coincident with PHPT. Further longitudinal data are needed to examine this population for inclusion in surgical criteria. In summary, for patients who meet biochemical criteria for the diagnosis of PHPT with a clearly demonstrable adenoma, careful consideration for the risk of future complications and expanded inclusion of an at-risk population should be weighed against the surgical risk and success when parathyroidectomy is performed by skilled surgeons.

Should Surgery Be Offered to All Correctly Diagnosed PHPT Patients?

If surgical correction is the only curative method, then should all single gland, biochemically defined patients be considered for parathyroidectomy, in particular minimally invasive surgery, in a skilled surgical facility? This approach would theoretically prevent long-term disease complications and decrease overall morbidity and need for repetitive testing during monitoring. In contrast, prospective trials have not shown symptom improvement in patients with mild PHPT; therefore, surgery cannot be recommended solely for the indication of suspected symptoms [54, 64].

To answer this question we must consider the age of the patient, the current clinical status of the patient's PHPT and most importantly, the effects of disease progression. Understanding disease progression is critical, since moving towards a consensus recommendation where surgery is considered for all asymptomatic or "classic" PHPT patients meeting biochemical criteria should be tempered by:

1. A careful examination for the spectrum of FHH biochemical profiles, given the estimated significant incidence of failed parathyroidectomy that may be due to misdiagnosed FHH and,
2. Asking if there is evidence for earlier intervention to reduce future sequelae including bone loss, fractures, kidney stones, and all cause mortality in patients who would otherwise be observed and medically managed.

The FHH Diagnostic Quandary

In differentiating FHH from PHPT the presence of low urine calcium or a low calcium/creatinine ratio are used to rule in FHH, or at least to increase suspicion. Despite these recommendations and estimates that upwards of 88 % specificity and 85 % sensitivity is obtained with a Ca/Cr <0.015 [55], an absolute "low" (<100 mg/24 h) 24-h urine calcium or a Ca/Cr <0.015 is not an absolute rule in/rule out differentiation point of FHH versus PHPT. Differences in dietary calcium, presence of Vitamin D3 deficiency, urine volume,

decline in GFR with age and renal acting medications can lead to misinterpretation of single 24-h urine calcium results. Repetitive testing, correction of Vitamin D3 and calcium deficiency, and removal of certain medications such as thiazides or calcium wasting diuretics (e.g., Furosemide) may be necessary to obtain a more trustable Ca/Cr result. Additionally, the presence of an adenoma is also not synonymous with PHPT since parathyroid enlargement has been found in FHH patients with CaSR mutations [56, 57]. This highlights a further dilemma since true adenomas or hyperplasia are found in a select few FHH patients. Careful examination of biochemical criteria, family history, urine calcium, and where appropriate, CaSR genotyping will aid in differentiating FHH from PHPT. Further work on examining the presentation and progression of specific CaSR genotypes will hopefully provide clinical guidance and consensus recommendations in the future. False positive imaging results that are seen in non-FHH patients also lend caution to a "surgery for all" approach [58], confirming that careful attention to the biochemical diagnosis is necessary prior to surgical intervention. Surgical and medical providers must balance diagnostic accuracy, patient presentation, short- and long-term medical risks, and the surgical risk of a parathyroidectomy to provide the patient with a consensus approach for optimizing outcomes while minimizing risks.

Current guidelines recognize the balance of this quandary, but outcomes data in small cohorts for >3–5 year follow-up do not yet support a recommendation for parathyroidectomy as the sole therapy for all asymptomatic, single-gland PHPT patients at their initial presentation.

Is There a Point Where Disease Progression and Mortality Risks Change in Observed PHPT Patients?

To examine this question, some studies have asked if there is a threshold after which continued medical management or observation is deleterious and surgery in those patients is more beneficial even if they do not meet surgical criteria. For mild PHPT there is not significant disease progression over a few (<3) years in some studies, but afterwards there may be significant changes in at-risk populations and overall mortality [24, 29, 49, 59]. For example, in a small cohort undergoing observation after 8 years there were statistically significant reductions in cortical BMD while significant increases in total serum calcium were present after 12 years [29]. Other studies noted changes in kidney stone incidence and decline of renal function [53, 60], while patients with mild PHPT without indications for surgery by current criteria had a significant increases in BMD at the spine and hip, but not the forearm nor in quality of life measures following surgical correction [11, 49]. These studies suggest pursuing parathyroidectomy in all correctly diagnosed patients with single-gland disease because it will likely decrease complications and potentially prevent skeletal progression, or kidney stones and renal function decline. This question requires more longitudinal study and discussion before a consensus opinion is reached on offering surgery to everyone, but based on eventual clinical progression and potentially increased mortality [24], there may be reasons to consider surgery in the appropriate patient even without current surgical criteria when they are diagnosed and operated on by experienced providers. These are areas for continued, careful discussion as to how to best resolve this question.

Medical Management in Nonsurgical Patients

Medical management can be done safely in some asymptomatic patients and in those where surgery is contraindicated, declined, or has failed to correct the hypercalcemia. Optimal monitoring focuses on the plasma calcium level and minimizing skeletal and renal complications. Current recommendations suggest a serum calcium, PTH, and 25(OH)D3 annually and a BMD every 1–2 years depending on the clinical severity or suspicion for bone loss [22]. Some physicians will monitor serum labs more frequently (every 4–6 months) depending on the severity of the hypercalcemia or comorbid conditions of the patient. Vitamin D3 can usually be safely replenished to a level of 30 ng/dL (75 nmol/L). Repleting Vitamin D3 may decrease PTH levels and improve bone density,

although in some studies this also increases hypercalciuria without increases in kidney stone formation [61]. Similarly, it is generally accepted that a normal calcium diet may reduce PTH levels and increase femoral neck BMD while restricting calcium may lead to further PTH increases and bone loss [62]. To manage the negative skeletal effects, bisphosphonates have been studied although with limited patients and for short durations. Positive effects on BMD with Alendronate at the hip and spine are known, but no fracture prevention data exist [63]. Little data exists for other bisphosphonates, Raloxifene or Denosumab. The use of Teriparatide is contraindicated in PHPT.

Cinacalcet has been extensively examined in PHPT for its effects on calcium lowering and increases in renal calcium excretion. Current recommendations place Cinacalcet as an approved therapy for PHPT and an effective method for lowering serum calcium in those patients with severe hypercalcemia or renal compromise or in whom surgery is contraindicated. Most do not recommend routine use of Cinacalcet in mild PHPT [22]. No direct effects on BMD are known and Cinacalcet use is often limited by overall cost.

Specific tailoring of pharmacologic therapy depends upon the goal of controlling calcium levels or stabilizing BMD. Risks of increased hypercalciuria and long-term risks of kidney stones are incomplete and require more study. Continued reassessment for surgical criteria and progression of disease is necessary in the medically managed PHPT patient. Further work on the progression of disease and management of its complications will guide future recommendations and hopefully address the issues of monitoring time and applied surgical criteria for single-gland asymptomatic PHPT.

Summary: Medical Management for Nonsurgically Treated Patients or in Whom Surgery Is Contraindicated

1. Routine monitoring of Plasma Calcium, PTH, 25(OH)D3, creatinine/GFR depending on the patients clinical condition and baseline renal function. Current guidelines suggest every 12 months, but this should be increased especially in patients with reduced renal function, significant comorbid conditions or when using renal acting and nephrotoxic medications.
2. Clinical assessment for complications of PHPT including new fractures, bone pain, and kidney stones.
3. A 3-site BMD assessment for bone loss every 1–2 years, depending on the clinical suspicion and other risk factors for increased loss rates.
4. Cautious management of calcium and Vitamin D3 intake to avoid deficiencies and promote positive effects on bone mineral density.
5. Use of medical therapy for bone maintenance (Alendronate) or hypercalcemia (Cinacalcet) in appropriate patients.
6. Continued reassessment for development of surgical criteria in patients who are surgical candidates or the need for more medical therapy in those who are unable to undergo surgery.

Safe medical management and observation in most PHPT patients is low risk and acceptable; however, analyses in some small longitudinal cohorts suggests a threshold for increased disease progression and complications. Continued reassessment for surgical inclusion criteria or further medical management in nonsurgical patients is necessary to minimize sequelae. Future work in defining threshold timing in the observed patient may lead to modification of the surgical approach. Current guidelines and recommendations are a group consensus between medical and surgical providers to optimize all facets of care for the PHPT patient and require continued, careful attention to disease-specific details to maximize therapeutic success rates in treating these patients

Society Guidelines
See above

Best Practices
See above

Expert Opinion

Single-gland asymptomatic PHPT is the most common form of PTH-dependent hypercalcemia. The disease process can present with or progress towards both skeletal and renal complications including bone density loss, fractures, nephrolithiasis, and decline in renal function. Differentiating PHPT from other overlap diagnoses, in particular FHH, by clinical and biochemical means is necessary before determining if a patient meets surgical criteria. The use of imaging should always be viewed with caution and applied only in correctly diagnosed patients. Although surgery is the only corrective therapy, a "surgery for all" correctly diagnosed patients recommendation has not yet reached consensus.

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6 Familial Hyperparathyroidism: Multiple Endocrine Neoplasia Types II and I; Familial Hypocalciuric Hypercalcemia; Hyperparathyroidism-Jaw Tumor Syndrome

Gayan S. De Silva, Terry C. Lairmore, and Jeffrey F. Moley

Contents

Familial hyperparathyroidism is associated with the Multiple Endocrine Neoplasia Syndromes (MEN). Two other syndromes, Familial Hypocalciuric Hypercalcemia (FHH) and Hyperparathyroidism-Jaw Tumor Syndrome (HPT-JT) are also hereditary forms of hyperparathyroidism (HPT). In the MEN syndromes, genetic changes in the MENIN and RET genes are responsible for the clinical presentations associated with the MEN type 1 and MEN type 2 syndrome, respectively. HPT-JT syndrome is caused by mutations in the HRPT2 gene and is characterized by parathyroid tumors and ossifying fibromas of the mandible and maxilla. FHH is caused by mutations in the gene for the calcium-sensing receptor, causing mild hypercalcemia and elevated parathyroid hormone (PTH) levels. The evaluation and treatment of these four clinical syndromes are described within this chapter.

MEN 1: Introduction

MEN1 is an autosomal dominant hereditary cancer syndrome arising from mutations in the MEN1 gene [1], which encodes the *menin* protein. Found on chromosome 11, the MEN1 gene encodes a 610 amino acid sequence, which is ubiquitously expressed in both endocrine and non-endocrine tissues with variable expression

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[2]. Known as a tumor suppressor gene, *menin* is also involved in multiple signaling pathways including gene transcription regulation, apoptosis, and cytoskeletal integrity. [3], and also has an important interaction as a coregulator of estrogen receptor α, implicating a role in the progression of breast cancer [4]. Female patients with MEN 1 are therefore at a theoretically higher risk for developing breast cancer [4].

The MEN 1 syndrome results from a germline heterozygous loss of function mutation, with most mutations in the gene resulting in the production of a shortened or nonfunctional protein [1]. Hundreds of mutations in Menin have been described in association with this syndrome (Fig. 6.1). Detection of MEN 1 mutation carriers can identify presymptomatic individuals in affected families, though there is controversy as to whether it is necessary to identify presymptomatic gene carriers, because there is no prophylactic surgery for the endocrinopathies that occur. In families with previously identified mutations, DNA testing is relatively straightforward as a direct test and is usually sufficient to identify the specific mutation. In patients with a new diagnosis of MEN 1, without previous family history, and with no knowledge of where the mutation might be, an extensive search through the coding sequences and beyond may be required to identify the mutation.

Given the autosomal dominant inheritance pattern, MEN 1 affects men and women equally, with a prevalence of 2–3 per 100,000 individuals [1]. The syndrome includes three primary disorders: hyperparathyroidism, adenomas of the anterior pituitary glands, and neuroendocrine tumors of the gastropancreatic system, i.e. insulinomas, gastrinomas, and glucagonomas [5]. Other tumors strongly associated with MEN 1 include lipomas, facial angiofibromas, collagenomas, thyroid and adrenal nodules, and foregut carcinoids. Endocrine neoplasms arising in the MEN 1 syndrome are generally characterized by earlier age of onset and are often multifocal. Hyperparathyroidism is the most common endocrine abnormality seen in patients with MEN 1, developing in greater than 90 % of individuals, and usually involves multiple glands. It often presents in the second to fourth decade of life, but has been reported as early as 5 years of age. This is in contrast to sporadic forms of hyperparathyroidism, which peak in the sixth decade [6]. Additionally, MEN 1 HPT has a high rate of recurrent hyperparathyroidism after technically and biochemically successful subtotal parathyroidectomy. This is due to the involvement of multiple glands, with all parathyroid tissue predisposed to hyperplasia. Asymmetric glandular enlargement is characteristic of patients with MEN 1 (Fig. 6.2), while fewer than 15 % of patients with sporadic hyperparathyroidism have multiglandular disease [7]. In one study, with a follow-up of 12 years, the recurrence rate was above 50 % [8].

Genetic testing and family counseling should be an integral part of the algorithm of treating patients with familial hyperparathyroidism, though ultimately clinical judgment and physician experience should dictate the type and timing of testing and treatment. Sequencing costs

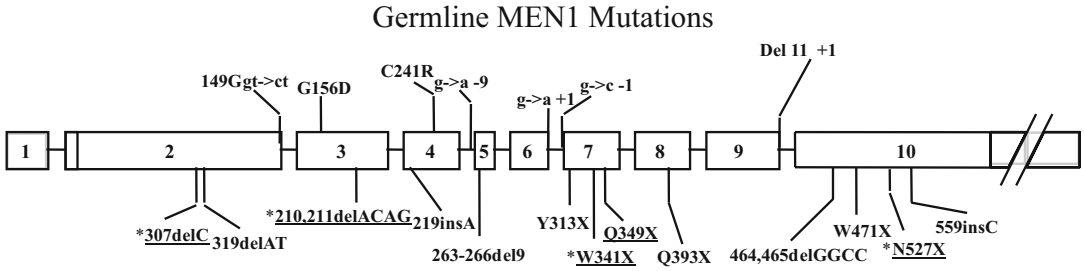

Fig. 6.1 Germline mutations in the MEN 1 gene. These mutations are distributed within the nine coding exons of the gene and include missense, nonsense, frameshift, etc. Above the depiction of the gene are five spicing defects and two missense mutations. Below the gene are seven nonsense and six frameshift mutations. Reproduced with permission from Mutch, M.G., et al., *Germline mutations in the multiple endocrine neoplasia type 1 gene*: *Evidence for frequent splicing defects*. Human Mutation, 1999. 13: 175–85

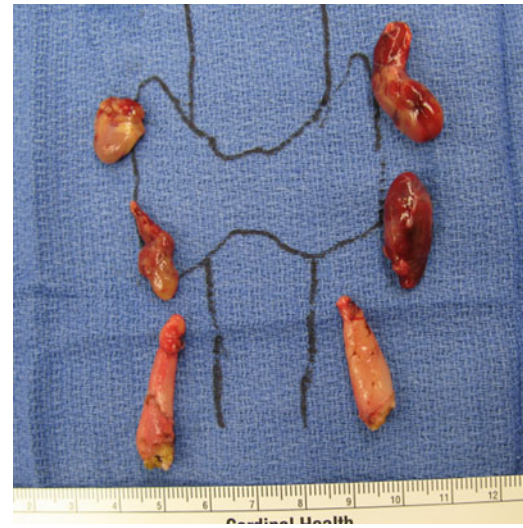

Fig. 6.2 Asymmetric parathyroid hyperplasia in MEN 1. Depicted are four parathyroid glands according to their in situ location within the neck along with the asymmetric hyperplasia commonly found in MEN 1 patients

continue to be relatively expensive and insurance programs often do not cover genetic testing. Yearly screening of calcium, prolactin, pancreatic polypeptide, and gastrin levels is recommended in at-risk MEN 1 family members. Consensus guidelines have been published and contain expert recommendations for evaluation, imaging, treatment, and follow-up for patients with MEN 1 [5]. Figure 6.3 contains a summary of recommendations for evaluation of these patients.

MEN 1: Treatment

In the biochemical evaluation of hyperparathyroidism, an elevated serum calcium level (hypercalcemia) is usually the first abnormality detected in patients with MEN 1. An inappropriately elevated parathyroid hormone (PTH) level in the setting of hypercalcemia confirms the diagnosis of hyperparathyroidism. Further evaluation may include measurement of elevated 24-h urine calcium if the diagnosis is still in question. One prospective study demonstrated that systematic screening of patients with MEN 1 showed a rapid rise in calcium levels between ages 10–15 years, before clinically evident disease [9], Fig. 6.4.

Preoperative parathyroid imaging in patients with MEN 1 should take into account the fact that at initial surgery all four glands and thymic horns should be identified intraoperatively. This falls outside of the "minimally invasive" algorithm. We only perform an ultrasound of the neck, mainly to look for thyroid gland pathology that may need to be addressed. To demonstrate the limitations of preoperative imaging in patients with multi-gland parathyroid disease, one retrospective study evaluated preoperative imaging and intraoperative parathyroid hormone monitoring to detect multi-gland disease (MGD) with the objective to assess the best predictor for detecting MGD [10]. Out of a cohort of 233 patients with hyperparathyroidism of all types, single gland disease (SGD) was found in 88 % and MGD in 10 %, with persistent hyperparathyroidism in 2.6 % of patients. For patients with operatively diagnosed MGD, preoperative sestamibi imaging correctly predicted MGD in only 2 of 23 patients, incorrectly showed SGD in 9 of 23 and was negative in 12 of 23. Ultrasound correctly predicting MGD in 6 of 23, incorrectly predicted SGD in 6 of 23, and was negative in 8 of 23 patients. Intraoperative PTH levels indicated MGD in 15 of 18 patients but falsely predicted cure after single gland excision in 3 of 18 patients.

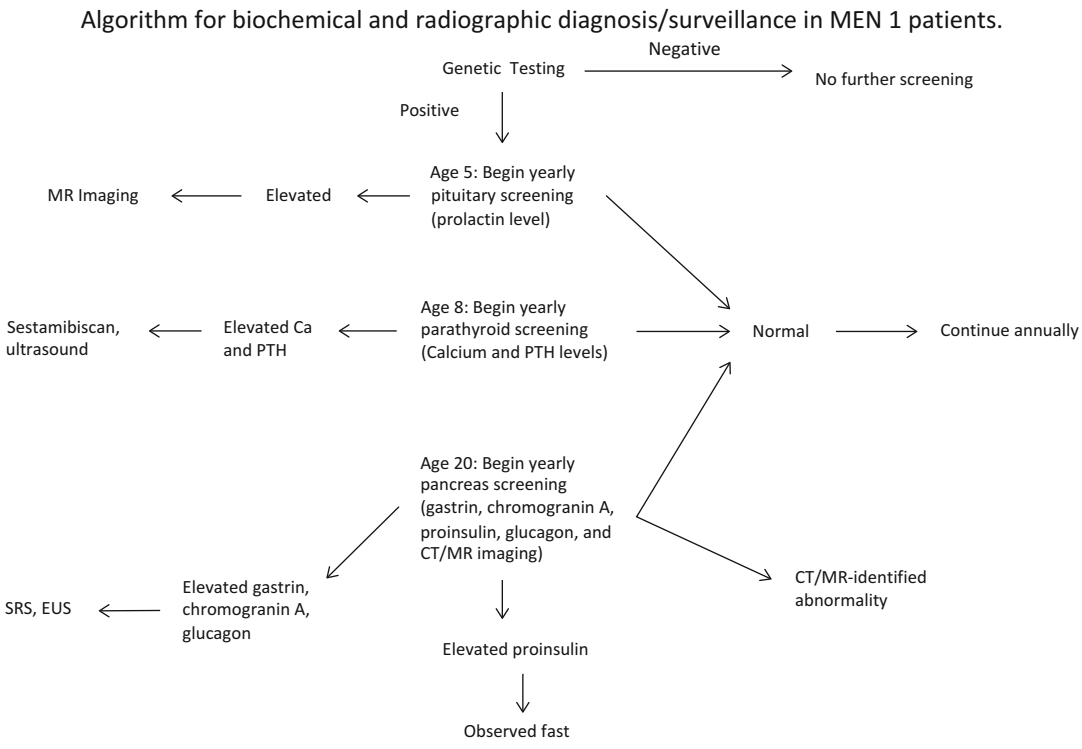

Fig. 6.3 Consensus guidelines for the clinical evaluation, genetic testing, imaging, and surveillance of MEN 1 patients. Reproduced with permission from Whaley JG, Lairmore TC. Multiple Endocrine Neoplasia Type 1: Current diagnosis and management. In: McGraw-Hill's manual of endocrine surgery, Morita SY, Dackiw APB, Zeiger MA (editors), McGraw-Hill Companies, Inc., New York, 2009

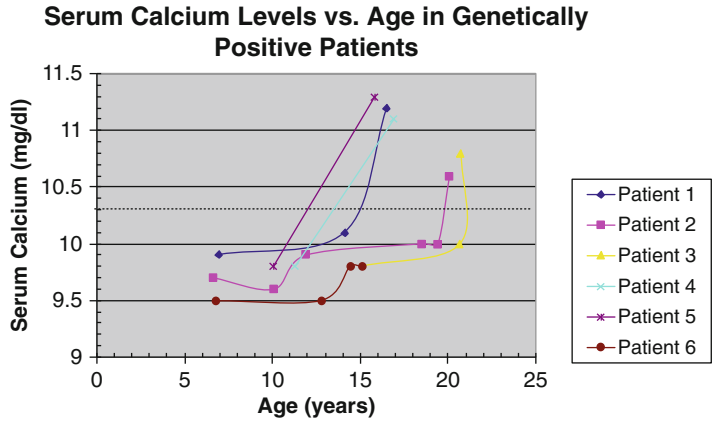

Fig. 6.4 Serum calcium levels vs. age in genetically positive patients. Prospective data demonstrating different time points in age (years) and serum calcium levels (mg/dl) for each patient. A rapid rise in calcium levels is evidence between the ages of 10–15 years, often before clinically evident disease. The *dotted line* demonstrates the upper-limit of normal serum calcium levels. Reproduced with permission from Lairmore TC, Piersall L, DeBenedetti M, Dilley W, Mutch M, Whelan A. Clinical genetic testing and early surgical intervention in patients with multiple endocrine neoplasia type 1 (MEN 1). Ann Surg, 2004. 239(5): 637–45; discussion 645-7

With all 3 modalities combined, the authors concluded MGD in 16 of 18 patients. In general, intra-op identification of all four parathyroid glands is standard in patients with MEN 1, along with serial measurement of intraoperative PTH levels.

There are two commonly utilized surgically procedures for the management of HPT in MEN 1: total parathyroidectomy with autotransplantation, and subtotal parathyroidectomy. Total parathyroidectomy is combined with heterotopic intramuscular autotransplantation, either in the sternocleidomastoid (SCM) or the brachioradialis muscle in the forearm [11]. This approach appropriately reduces the volume of parathyroid tissue in an attempt to achieve normal calcium levels, while the auto-transplantation of parathyroid tissue in a vascular skeletal muscle bed allows simple access for further parathyroid tissue reduction (in the setting of recurrent hyperparathyroidism). The second approach involves performing a subtotal parathyroidectomy (3.5 glands), while leaving a viable parathyroid gland remnant on a vascular pedicle [12]. This approach also reduces the volume of functional parathyroid tissue in the neck and results in normalization of calcium level, without the need for auto-transplantation, which entails a period of about 6 weeks for the transplanted parathyroid fragments to function adequately. Regardless of which approach utilized, the surgeon should make an effort to identify all four parathyroid glands as well as supernumerary or ectopic glands. The thymic horns should also be removed because additional parathyroid tissue may be present in these structures in MEN 1 patients. Multiple studies have demonstrated similar rates of recurrent hyperparathyroidism, and permanent postoperative hypoparathyroidism and associated hypocalcemia with either procedure [13–22]. One randomized prospective trial compared total parathyroidectomy with autotransplantation to subtotal parathyroidectomy in MEN 1 patients. No significant differences in rates of permanent hypoparathyroidism or recurrent hyperparathyroidism were noted [23].

Parathyroidectomy in MEN 1 has a higher risk of postoperative hypoparathyroidism and recurrent hyperparathyroidism when compared with parathyroidectomy for sporadic cases. To address the issue of postoperative hypoparathyroidism and symptomatic postoperative hypocalcemia, high volume centers with Good Medical Practice (GMP) capability utilize cryopreservation of autologous parathyroid tissue at the time of the index operation. This tissue can be transplanted back into the patient if transplanted autografts do not work, or if the viable parathyroid fragment fails. In one study that examined the functionality of delayed cryopreserved parathyroid autografts, however, the authors found that only 60 % of these delayed autografts showed evidence of graft function (based on venous PTH sampling) when comparing grafted versus nongrafted limbs. Additionally, 40 % of patients receiving delayed cryopreserved autografts resolved their postoperative hypocalcemia, and required no further calcium supplementation [24]. It is best to do a successful operation the first time.

In cases of recurrent or persistent MEN1 hyperparathyroidism, it is extremely important to carefully review the previous operative notes and pathology reports to figure out exactly what was done at the initial operation. If the patient has parathyroid autografts in the forearm, parathyroid hormone gradients calculated from levels obtained from basilic vein blood draws from each arm, will help localize the source. If there is a large gradient in the grafted arm, then hyperplasia of the autografts is the likely source. If not, there may be hyperfunctioning parathyroid tissue left in the neck, and imaging with sestamibi scanning, ultrasound, and computed tomography of the neck and chest should be done. Sestamibi scanning should include the grafted forearm.

MEN 2: Introduction

MEN 2 syndromes include MEN 2A and MEN 2B. Familial non-MEN medullary thyroid carcinoma (FMTC) is now considered a sub-type of MEN 2A. The prevalence is approximately 1 per 30,000 [25]. The hallmark disease of the MEN 2 syndromes is medullary thyroid carcinoma (MTC), which occurs in near total penetrance in

affected families [25]. MEN 2 syndromes are caused by activating mutations in the RET proto-oncogene, found on chromosome 10, and are autosomal dominant [26]. The RET gene encodes a tyrosine kinase protein involved in multiple functions of cellular growth and differentiation of tissues, and is variably expressed in tissues of neural crest origin. These include the parafollicular C-cells of the thyroid, parathyroid glands, and adrenal enterochromaffin cells. The genetic and cellular basis for the MEN 2 phenotype is gain of function in the protein product of RET, rather than loss of function, as is seen in MEN 1.

The classic constellation of disease processes in MEN 2A includes medullary thyroid carcinoma (MTC), adrenal medullary hyperplasia with pheochromocytoma, and hyperparathyroidism. MEN 2B includes medullary thyroid carcinoma, pheochromocytomas, and mucosal neuromas. Genetic testing is an important part of the workup in the assessment of patients with suspected MEN 2 syndrome, and the clinical features and tumor behavior are closely related to the specific RET germ-line mutation present. The mainstay for treatment in patients with MEN 2, with early identification of germ-line mutations in the RET gene, is prophylactic thyroidectomy to prevent medullary thyroid carcinoma. The role of surgery and management of hyperparathyroidism in the setting of MEN 2 is discussed below.

While virtually all patients who inherit a germ-line mutation in the RET proto-oncogene will develop MTC during their lifetime, primary hyperparathyroidism develops in only 10–25 % of MEN 2A patients [25, 27], and occurs mostly in patients with specific mutations. Mutations in codons 609, 611, 618, 620, 631, 634, 791, and 804 of RET are associated with hyperparathyroidism. As with MEN 1, multi-gland disease is common [27], and is found in 80 % of patients with hyperparathyroidism in MEN 2A. The most commonly associated mutation associated with hyperparathyroidism in MEN2A is a C634R mutation [28]. Routine screening for hyperparathyroidism in patients with MEN 2A should include annual serum calcium levels, with an elevated level followed up with PTH measurement.

MEN 2A: Treatment

The goal of preventative surgery for patients with MEN 2A and 2B is well established, because the development of MTC is almost 100 % in carriers of MEN 2 germline mutations. Current evidence supports preventative surgery in the first year of life for patients with MEN 2B, and by the age of 5 or 6 or patients with MEN 2A, though there is controversy regarding this [25]. Preservation of parathyroid glands in preventative thyroidectomy in children can be very difficult given their small size, appearance, and prominent thymic and nodal tissue (Fig. 6.5). These procedures should only be done by experienced surgeons. Additionally, the pursuit of an appropriate central node dissection compromises the blood supply to the parathyroid glands (inferior thyroid artery). Preservation of parathyroid function may be accomplished by either careful preservation on an intact vascular pedicle, or autotransplantation of minced devascularized glands. Parathyroid glands should be minced into 1 × 1 mm fragments and fragments transplanted into multiple individual muscle pockets, with ~2–3 fragments per pocket. This exposes the fragmented parathyroid

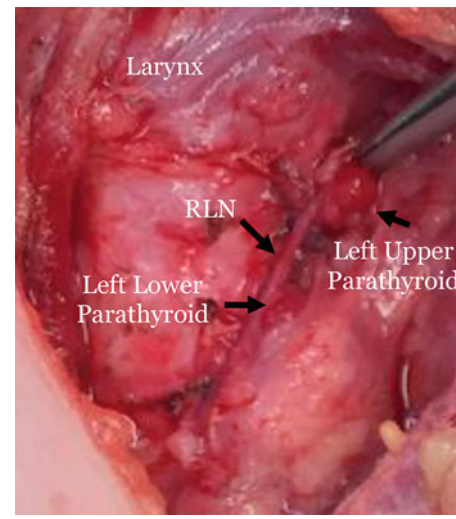

Fig. 6.5 Post-procedure operative bed in an MEN 2A patient at 2.5 years of age. Depicted here is relationship between the recurrent laryngeal nerve (RLN) and the left upper and left lower parathyroid glands. Note the diminutive size of the glands, as well as the size of the RLN

glands to a bed of well-vascularized skeletal muscle, with an increase in available surface area [29]. Experiences at high volume centers in patients with MEN 2A have demonstrated that total thyroidectomy, central node dissection, and total parathyroidectomy with auto-transplantation of parathyroid tissue into the nondominant forearm is safe, and long term disease control was excellent, with normal parathyroid function in 47/50 patients with no need for supplementation [29]. Follow-up studies demonstrated that nodal metastases is rare in MEN 2A <8 years of age and in patients with basal calcitonin levels less than 40 pg/ml [29, 30]—compelling a change in practice to perform total thyroidectomies and leave parathyroid glands in-situ if possible if the above conditions are met, assuming that there are no PTH abnormalities at the time of surgery. Interestingly, one study demonstrated that hyperparathyroidism did not develop in any of their 27 patients treated with early thyroidectomy [31], though the reasons for this currently remain unclear.

If the parathyroid glands are left in-situ and the patient develops subsequent hyperparathyroidism, imaging with sestamibi scan, ultrasound, and computed tomography should be done to localize the hyperfunctioning gland or glands. The approach to these patients is similar to MEN 1 patients, described previously. Bilateral neck exploration with identification of all remaining parathyroid glands may be necessary, and intraoperative parathyroid hormone monitoring should be used to ensure correction. As with MEN 1, surgical options include a subtotal parathyroidectomy (3.5 gland), total parathyroidectomy, or removal of only abnormal appearing glands [25]. The optimal surgical management remains controversial [32], however, as some specialist argue for the removal of only abnormal glands, while others advocate for a subtotal parathyroidectomy and leave a ½ gland remnant on a well vascularized pedicle. Other experts prefer total parathyroidectomy with auto-transplantation into the nondominant forearm muscle, even in the presence of normal appearing parathyroid tissue. This is due to the assumption that eventual parathyroid hyperplasia in normal appearing glands is high and provides the advantage that the forearm autograft is theoretically more easily accessible in cases recurrent hyperparathyroidism. Transplantation to the forearm theoretically prevents a reexploration of the neck. A recently published study by our group examined total parathyroidectomy with autotransplantation vs. an in situ preservation approach. Patients in the in situ group had parathyroid autotransplantation only if parathyroids were devasularized during surgery. Follow-up results demonstrated permanent hypoparathyroidism in 3/50 (6 %) patients in the total parathyroidectomy/forearm transplant group, and 1 of 102 (<1 %) patients in the in situ group. The authors therefore concluded that successful preservation of parathyroids in situ during preventative thyroidectomy (the authors performed central neck dissection only if the serum calcitonin >40 pg/ml) was a safe and effective alternative [33]. Irrespective of the surgical treatment, the general consensus is that institutional preference should be followed, as recurrence rates are generally low, whether in performing subtotal parathyroidectomy, or total parathyroidectomy [29, 32].

Hyperparathyroidism-Jaw Tumor Syndrome: Introduction

HPT-JT is an autosomal dominant disorder caused by mutations in the HRPT2 gene, found on chromosome 1 [34]. HRPT2 encodes a 531 amino acid protein and is thought to act as a tumor-suppressor gene. Mutations in the HRPT2 gene reduce expression and/or function of the nuclear protein parafibromin (aka cell division cycle 73—CDC73), a regulator of gene expression and inhibitor of cellular proliferation [35, 36]. Further studies demonstrated that a high number of these mutations resulted in a premature truncated protein with loss of function [37]. Currently, there are 111 recognized mutations: 68 germline, 38 somatic, and 5 with an origin that is not yet defined [38]. Of these, germline frameshift mutations and nonsense mutations account for the majority (88 %) of identified mutations in HRPT2 HPT-JT [39].

One of the earliest reports of HPT-JT came from a case report in 1958 [40] that described a multigenerational family with hyperparathyroidism in which four of five affected first generation members developed jaw tumors. Additionally, three members of the third generation (with HPT) also developed jaw tumors, which appeared after parathyroidectomy. These jaw tumors were histologically distinct from the classic hyperparathyroid-associated "brown tumors". Brown tumors generally represent a reparative process secondary to heavy osteoclast activity. Histology usually demonstrates fibrous tissue, woven bone, evidence of angiogenesis, granulation tissue, giant cells, osteoblasts and osteoclasts, and deposition of hemosiderin [41]. The lesions seen in the family were fibro-osseous appearing, lacked giant cells, and appeared histologically different from brown tumors.

The clinical presentation of HPT-JT includes parathyroid tumors (adenomas and carcinomas), uterine tumors, ossifying jaw tumors, and renal abnormalities [36, 42]. The most common initial presentation in HPT-JT is primary hyperparathyroidism, with a penetrance of 80–90 %, and often manifests in the third decade of life [43]. Parathyroid adenomas often occur asynchronously in HPT-JT [36] and while most tumors are benign, the risk of malignant transformation is higher than in nonfamilial HPT adenomas. With a reported incidence of 15 %, parathyroid carcinoma is of clinical concern in patients with HPT-JT [44] compared to <1 % in other forms of primary HPT. One study examining germline and somatic mutations in HRPT2 in the setting of sporadic parathyroid carcinomas found that 10 of 15 patients had HRPT2 mutations, and while they did not specifically examine the linkage between these mutations and known mutations in HPT-JT, they concluded that patients with apparently sporadic parathyroid carcinoma, who carry germline mutations in HRPT2 may have evidence of HPT-JT syndrome, or phenotypic variants [45]. This is supported by another study that demonstrated that a small minority of patients (2 of 7) with apparently sporadic parathyroid carcinoma, carried a germline HRPT2 mutation—suggesting they may have occult HPT-JT [46]. Unlike the high level of penetrance of hyperparathyroidism in HPT-JT, renal abnormalities are only seen in approximately 5–15 % of patients, with cystic kidney disease being the most common [47]. Unlike sporadic forms of hyperparathyroidism or familial HPT in MEN 1 or 2A, patients with HPT-JT can also develop renal anomalies including renal cysts, adult onset Wilms' tumor, and hamartomas [42]. Another feature of HPT-JT is the development of uterine tumors. These have been described as affecting up to 75 % of females with HPT-JT [48]. Uterine tumors in HPT-JT may be malignant or benign, and include adenosarcomas (2/15), adenofibromas (5/15), leiomyomas (4/15), adenomyosis (8/15), and endometrial hyperplasia, (4/15). Some women had more than one uterine pathology [48].

HPT-JT: Treatment

As with most cases of familial hyperparathyroidism, the mainstay choice of treatment is surgical resection; however, given the relatively low prevalence of the disease, the potential for future asynchronous adenomas, and the risk of parathyroid carcinoma, the best surgical management remains controversial. One option is prophylactic total parathyroidectomy at the index operation for single gland adenoma, as a means to reduce the risks of malignant transformation and parathyroid carcinoma. However, this poses two problems—the first parathyroid carcinoma in HPT-JT continues to be an evolving area of study, and the number of cases is relatively small and the second is the risk of permanent hypoparathyroidism. Some surgeons may opt to utilize localizing imaging studies, i.e. ultrasound, SPECT/CT with 99m-Tc-sestamibi scanning, MRI, etc. to identify single gland disease as opposed to standard bilateral neck exploration. Intraoperative PTH measurement should continue to be a mainstay of surgical evaluation, especially since HPT-JT patients may have supernumerary parathyroid glands. If parathyroid carcinoma is encountered at the time of the first operation, or any reoperation, standard

management is for en bloc tumor resection, ipsilateral thyroid lobectomy, and resection of the adjacent soft tissue bed (central neck dissection) [49]. Grossly, parathyroid carcinomas appear much larger than parathyroid adenomas (up to 3.5 cm vs. 1.5 cm, respectively), and can be palpable on physical examination. With the possibility of recurrent hyperparathyroidism due to asynchronous parathyroid adenomas, some centers advocate for subtotal parathyroidectomy at the time of the initial operation. One study demonstrated that 80 % of individuals with germline mutations in HRPT2 had persistent or recurrent hyperparathyroidism after focused parathyroidectomy [50].

Familial Hypocalciuric Hypercalcemia

FHH is an autosomal dominant disorder characterized by inactivating mutations in the gene encoding the calcium-sensing receptor (CaSR), found on the long arm of chromosome 3 (3q21.1) [51]. The gene codes for a 1078 amino acid membrane spanning protein that senses extracellular calcium levels. Other variants of FHH (FHH2 and FHH3) result from mutations on the short and long arm of chromosome 19 (19p13.3 and 19q13.3), respectively [52, 53]. This receptor is expressed in multiple tissue types, including the parathyroid glands, kidney, bone, osteoclasts, osteoblasts, thyroid C-cells, and others, and one of its major functions is to regulate calcium homeostasis [54].

In the parathyroid gland, CaSR is highly expressed on the surface of chief cells, and senses small changes in serum calcium levels, allowing the parathyroid gland to produce an appropriate amount of parathyroid hormone to regulate calcium homeostasis. Activating or inactivating gene mutations that affect the sensitivity of the CaSR alter the regulation of PTH production. Of the ~200 CaSR gene mutations that have been identified, most result in a single missense mutation, creating a receptor protein with relative insensitivity to serum calcium levels [55]. In FHH, a heterozygous loss of function results in a CaSR protein that is desensitized to serum calcium levels; the patient therefore develops lifelong compensatory hypercalcemia [51]. In normal individuals with intact CaSR, hypercalcemia would lead to suppression of PTH gene expression; however, in FHH, compared to normal individuals, the set point for PTH suppression is higher at any given calcium level, resulting in slightly higher than normal levels of PTH production [55], though most patients with FHH will only demonstrate normal or slightly above normal levels of PTH.

Patients with FHH rarely have symptoms of hypercalcemia (constipation, nephrolithiasis, nephrocalcinosis, bone pain, etc.) and hyperparathyroidism. Documented complications of FHH are pancreatitis and chondrocalcinosis, though these are also rare [56, 57]. Distinguishing hyperparathyroidism in FHH vs. patients who have sporadic HPT, MEN HPT, or HPT-JT is important, as FHH does not usually require parathyroid surgery, though atypical presentations of primary hyperparathyroidism and FHH can be difficult to diagnose. Approximately 10 % of patients with primary hyperparathyroidism will have elevated calcium levels with relatively normal PTH levels, while 15–20 % of patients with FHH may have mildly elevated PTH levels. A low 24 h urine Calcium with a Ca/Cr ratio of <0.01 % is usually indicative of FHH, and sequencing of the CASR is definitive. Often times, however, the Ca/Cr clearance ratio can be misleading, because some patients with primary HPT will have a clearance ratio of 0.01–0.03. Some family members with FHH will demonstrate some degree of hypercalciuria [58]. In patient populations where a biochemical diagnosis is difficult or ambiguous, genetic analysis may distinguish atypical primary HPT from FHH, especially in the setting of overlapping Ca/Cr clearance ratios, index FHH patients, families with a history of isolated hyperparathyroidism, etc.

As previously mentioned, because the natural history of FHH is usually benign, patients should not undergo routine subtotal parathyroidectomy or any aggressive intervention, unless patients demonstrate a rare localized adenoma or persistent symptomatic hypercalcemia.

Best Practices: N/A

Society Guidelines: N/A

Expert Opinion

An awareness of genetic and syndromic causes of hyperparathyroidism is essential for all parathyroid practitioners. A lack of appreciation of these well-described etiologies of hyperparathyroidism can often be root causes for ambiguous laboratory testing and/or pre-operative imaging as well as operative failure. For these reasons, as well as to provide comprehensive care to patient relatives, it is of paramount importance to be acquainted with the genetics and syndromes described in this chapter and be vigilant for them at the start of each new patient encounter or as a possible explanation for failed surgical cases or delayed recurrent hyperparathyroidism.

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Secondary Hyperparathyroidism

7

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Introduction

Patients with chronic renal disease often times have derangements in calcium and phosphorus levels with resultant increases in PTH. These abnormalities in mineral metabolism are important determinants of bone and cardiovascular health. The current Kidney Disease: Improving Global Outcome (KDIGO) guidelines recommend individualized treatment and targets. This chapter reviews the action of PTH and calcium regulation as well as the pathogenesis, etiology, and treatment of secondary hyperparathyroidism of renal origin.

Physiology of PTH Action and Calcium Regulation

The parathyroid hormone is a single-peptide chain consisting of 84 amino acids. The amino terminal portion of this molecule is predominantly responsible for its actions. The rate of clearance of the 1–84, biologically active, amino acid peptide is faster than the inactive fragments. Earlier assays only provided an insight into the gland activity and not necessarily the function as they measured both the active and inactive fragments. The newer double antibody assays that are more widely used these days, measure only the intact fragment.

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The primary function of parathyroid hormone (PTH) is the maintenance of the extracellular calcium concentration. Parathyroid hormone acts directly on the bone and kidney and indirectly on the intestine in order to maintain calcium homeostasis. As extracellular calcium concentrations decline and PTH levels rise, there is release of calcium from the bone into the blood. At the level of the kidney, PTH exerts its effect by increasing reabsorption of calcium from the glomerulus. Indirectly, PTH increases the production of 1, 25(OH) D2 which in turn increases the intestinal absorption of calcium. The action of PTH on these organs is critical in maintaining calcium homeostasis. Ionized calcium is the most important determinant of PTH secretion. In addition to hypocalcemia, mild hypomagnesemia, hyperphosphatemia, and low calcitriol levels stimulate the secretion of parathyroid hormone.

Hypocalcemia results in an increase in the level of parathyroid hormone up to five times the basal rates of secretion. This in turn results in (1) increase in the calcium release from bone into the blood, (2) increased calcium reabsorption at the level of the kidney and (3) vitamin D mediated increased absorption of calcium through the intestines. The parathyroid glands are stimulated via a calcium sensor, a G protein-linked receptor located on the plasma membrane of the parathyroid glands. Under conditions where all glands are functioning normally, excesses in calcium concentration are effectively corrected by the changes in parathyroid levels. The decline in calcium levels is counteracted by an increase in the secretion of parathyroid hormone. In situations where the organs are unable to function normally, such as in kidney disease, the elevations in PTH fail to maintain calcium and phosphate homeostasis and secondary hyperparathyroidism ensues.

In chronic kidney disease, due to a decrease in renal mass and subsequent depletion of 1 α hydroxylase, the production of 1, 25(OH) D2 (calcitriol) is decreased and phosphate levels increase due to impaired phosphate excretion. The phosphatonin fibroblast growth factor FGF23 also increases which in turn down regulates the enzyme 1 α hydroxylase and thereby exacerbates the deficiency of calcitriol. This leads to hypocalcemia and as an adaptive response, the parathyroid levels increase. Continuous stimulation of the parathyroid gland results in diffuse polyclonal hyperplasia followed by monoclonal nodular hyperplasia [1, 2]. In early kidney disease, abnormalities in mineral metabolism are not frequently observed. It is likely that FGF23 plays a role in maintaining this calcium and phosphate homeostasis [3]. FGF-23 reduces serum phosphate by directly inhibiting the phosphate absorption in the proximal tubule and indirectly by decreasing calcitriol synthesis. As kidney disease advances, the above mechanisms are unable to maintain the phosphate balance. The resultant hyperphosphatemia that ensues may cause extra osseous deposition of calcium and phosphate. In SHPT of renal origin, calcium levels are often within or below the reference range. Uremia may further affect the calcium levels by impairing the intestinal absorption of calcium.

FGF23 decreases PTH secretion and cell proliferation in normal glands but it does not have an effect on a hyperplastic gland. Parathyroid hormone levels begin to rise once creatinine clearance falls below 80 mL/min [4].

Klotho is a transmembrane protein with decreased production in CKD and is likely responsible for the changes in vasculature, bone and skin in these individuals. In the kidneys, this gene is located on the proximal tubule cells, brush border, and urinary lumen. Klotho acts as a cofactor for FGF23, and regulates phosphate metabolism. In the absence of Klotho, FGF23 signaling is impaired [5]. It is postulated that the decline in Klotho causes resistance of FGF23 actions on the kidney and the parathyroid gland. As a result, FGF23 levels continue to rise, further increasing PTH and reducing vitamin D. This results in a vicious cycle and contributes to the progression of SHPT in CKD. Elevations in calcium and phosphate levels associated with SHPT may result in vascular calcifications and an increase in morbidity as well as mortality. The high FGF23 levels seen in CKD and are associated with increased all-cause mortality in hemodialysis patients as well as poor cardiovascular outcomes [6–8].

Physiology of Vitamin D

Upon exposure to sunlight, ultraviolet radiation enters the epidermis and 7-dehydrocholesterol is converted to pre-vitamin D3. This compound is biologically inactive and within 24 h, it is converted to Vitamin D3 in the epidermis. In the presence of vitamin D binding proteins, the synthesized Vitamin D is translocated into the circulation. From there, it is transported to the liver and metabolized to 25OHD by hepatic enzymes. 25OHD is not active at physiologic levels. It is transported to the kidney for additional hydroxylation. The kidney plays a vital role in the conversion of 25OHD to an active metabolite 1, 25, (OH) D2 by the enzyme 1 alpha hydroxylase. In the presence of hypocalcemia, PTH normally stimulates the synthesis of 1,25(OH)2D. In mild to moderate renal failure EGFR > 30 ml/min, hyperphosphatemia and decreased phosphate clearance suppress 1,25(OH) D2. This occurs even despite the elevation seen in PTH.

Clinical History and Diagnosis

In SHPT, calcium levels are usually normal to slightly low and individuals may be asymptomatic. Symptoms include mild perioral numbness and tingling, cramping in hands and feet. Uremic symptoms may also be noted. Chvostek and Trousseau's sign is positive on physical examination. Often times the cause of hypocalcemia is obtained from the history itself. In Table 7.1, we have shown the causes for secondary hypoparathyroidism and the appropriate test where applicable to help in the diagnosis.

In the case of SHPT due to renal disease, additional history of renal insufficiency, serum creatinine, phosphorus, BUN, assessment of urine output, and comorbidities is essential. The measurement of PTH is required and is typically high in the presence of a normal to mildly low serum calcium concentration. Due to the chronicity of the disease, serum albumin should be routinely measured to obtain a corrected calcium level. Elevated serum calcium excludes SHPT of renal origin.

Guidelines for the Management of SHPT

Treatment of SHPT is aimed at minimizing all-cause morbidity and mortality, abnormal mineral metabolism, and bone disease as well as preventing extra-skeletal calcium deposits including vascular calcification.

In 2009, the Kidney Disease: Improving Global Outcome (KDIGO) developed practice guidelines which provided recommendations for the evaluation and management of chronic kidney disease-mineral and bone disorder (CKD-MBD). The KDIGO does not recommend specific targets for PTH based on the stage of renal disease. They recommend using intact PTH as an assay. There is a greater momentum towards early detection and treatment of SHPT. In CKD stage III {GFR 30–59 mL/min/1.73 m^2] PTH should be monitored every 12 months along with annual calcium and phosphorus assessments. Therapy should be initiated if the PTH rises steadily or persistently remains above the upper limit of normal. In CKD stage IV [GFR 15–29 mL/min/1.73 m^2], PTH measurements are recommended every 3 months. In CKD V not yet on dialysis, PTH should be assessed every 3 months while calcium and phosphorus levels are assessed monthly. The goal is to maintain calcium and phosphorus levels within the normal range.

In 2003, the Kidney Disease Outcome Quality Initiative KDOQI specified target goals for PTH, calcium, and phosphorus. For patients with CKD stage V [below 15 mL/min/1.73 m^2], the KDOQI guidelines recommended a target intact PTH (first-generation immunometric assay) of between 150 and 300 pg/mL, calcium phosphorus product of less than 55, serum calcium in the lower half of the normal range [8.4–9.5 mg/dL] and serum phosphorus between 3.5 and 5.5 mg/dL. The standard treatments used in order to achieve these targets were limited by drug side effects and thus these goals remained largely unmet [9].

The newer KDIGO CKD-MBD guidelines have used more of an evidence-based approach and have individualized treatment and represent the most current clinical management guidelines.

Table 7.1 Differential diagnosis, clinical features, and testing for common causes of SHPT

Cause	Clinical features	Diagnostic test
Impaired intestinal calcium absorption		
Low dietary intake	Avoidance of dairy products/ obtained via history	24 h urine calcium assessment
Lactose intolerance	Abdominal pain, bloating, flatulence, diarrhea, bulky, frothy, and watery stools Known history of lactose intolerance	Lactose tolerance test Lactose Breath Hydrogen tests ? genetic testing
Decreased intestinal absorption		
Celiac disease	Diarrhea, weight loss, associated autoimmune diseases such as Crohn's disease, T1DM	Transglutaminase antibodies Endomysial Ab Intestinal Biopsy Evaluate for iron and B12 deficiencies
Pancreatic steatorrhea	Mild GI symptoms	Stool studies for fat Evaluate for iron and B12 deficiencies
Vitamin D deficiency		
Sunlight deprivation	Lack of sun exposure especially high-risk groups (elderly, nursing home residents) religious beliefs Use of sunscreens	25OHD
Intestinal Vitamin D malabsorption	Liver disease	Hepatic function
Loss of calcium related to the following disease		
Bone	History of bisphosphonate use in: Paget's disease Osteoporosis Bone metastasis	NA
Lactation	Obtained via history/recent history of weaning	NA
Kidney	History of kidney stones, loop diuretics, family history of kidney stones	24 h urine studies for calcium, sodium, phosphorus, oxalate, citrate
Soft tissue damage	Traumatic muscle damage, ICU stay, extensive burns	CK levels
Impaired PTH secretion		
Renal failure	Pruritus, anuria, uremic symptoms, anemia	Creatinine, phosphorus, blood urea nitrogen
Pseudohypoparathyroidism	Albright phenotype Family history Tetany	Genetic testing

Target PTH levels should be based on the levels of renal dysfunction to avoid high bone turnover and maintain near normal levels of alkaline phosphatase. This goal can be achieved by keeping PTH near the upper limit of normal in CKD stages 3–4 and up to nine times normal in the dialysis population [10]. However, a uniform classification system in this area is lacking.

Current KDIGO guidelines do not recommend routine measurements of bone mineral density in CKD, although suggest that serum PTH or bone-specific alkaline phosphatase levels should be assessed to predict bone turnover [10].

Bone biopsy is the gold standard procedure to assess CKD-MBD but is invasive and not widely available. Vascular calcification can be assessed

by lateral abdominal radiograph, echocardiogram, or computed tomography (CT) scanning.

Treatment of SHPT

The goal of treatment is to lower PTH while maintaining normal calcium and phosphorus levels. This is often times very challenging due to the complex interrelationship of hormones, bone health, diet, and mineral balances within the body. It is to be kept in mind that the treatment options discussed below improve biochemical parameters and bone histology although the evidence on the impact on patient-related outcomes is lacking.

The use of standard treatment measures such as calcium supplementation, phosphate binders, and vitamin D analogs are limited by the development of hypercalcemia, hyperphosphatemia, increased Ca×P product with resultant increase in vascular calcifications.

Calcium Supplements

Calcium supplements are only moderately effective in controlling PTH levels in those with SHPT on dialysis or early stages of renal failure. Calcium carbonate alone versus oral or IV calcitriol did not show a significant decrease in the levels of PTH [11, 12]. High doses of calcium supplementation are limited by calcifications that occur once the Ca X P product exceeds 55. Calcium supplements are limited to 1–2 g per day due to this concern.

Restriction of Dietary Phosphorus and Phosphate Binders

The mainstay of treatment is the correction of hyperphosphatemia and prevention of a positive phosphate balance. This in turn limits the development of hyperparathyroidism and its related effects.

Phosphate control is still an unmet need in CKD. Serum phosphorus is an independent risk factor for mortality in ESRD [13, 14] In mild CKD, restriction of dietary phosphate reduces PTH levels [15]. Phosphate restriction can be achieved via eliminating food preservatives and other additives. In order to maintain a balance between protein and phosphorus levels, foods with high biological value such as eggs and meats are preferred. Phosphorus intake should be limited to 900 mg/day.

In addition to dietary interventions, phosphate binders are used to control serum phosphate levels. As the disease advances, dietary restriction alone is insufficient to reduce hyperphosphatemia and the resultant SHPT. The currently available phosphate binders bind about 250 mg/day of phosphate [16]. With use of a single phosphate binder, about 30–50 % of ESRD patients remain hyperphosphatemic. Combination therapy with two different binders, increases the phosphate binding capacity and maintains serum phosphorus levels within acceptable ranges. Both calcium and non-calcium-based phosphate binders have been used in the treatment of SHPT. Aluminum is no longer used due to its serious toxicities. The use of calcium-based binders increase the risk of hypercalcemia, calciphylaxis, and vascular calcification [17]. The calcium free phosphate binders such as, sevelamer and lanthanum carbonate, decrease serum phosphate levels without causing hypercalcemia but they are not potent in lowering PTH levels [18]. Ferric citrate is an iron-based oral phosphate binder that effectively lowers serum phosphorus levels and has been shown to have safety profile similar to sevelamer and calcium acetate in hemodialysis patient [19]. Niacin reduces phosphate absorption by blocking the active sodium-phosphate co-transporters in the small intestines and has shown promising results [20]. Calcium containing binders are less costly and readily available and can be used in patients with CKD who have hypocalcemia. Non calcium containing phosphate binders are preferred in individuals with CKD and normal or high calcium levels.

Calcium as well as non-calcium-containing phosphate binders were shown to comparably lower FGF23 levels [21]. Overall, both calcium and non-calcium phosphate binders are shown to

be effective in lowering phosphorus levels but the impact of these agents on all-cause mortality and cardiovascular mortality in CKD is unclear [22]. In a recently published meta-analysis, non-calcium-containing phosphate binders were associated with lower all-cause mortality [23]. Available phosphate binders can increase calcifications in coronary artery and abdominal aorta [24]. Dietary phosphate restriction, with or without calcium carbonate treatment, resulted in progression of vascular calcifications, although this effect was not seen in those treated with sevelamer [25]. However, data supporting improved clinical outcomes by limiting the progression of vascular calcifications is lacking.

Vitamin D and VDR Agonist

Adequate levels of vitamin D are required for intestinal absorption of calcium. In the presence of low vitamin D, intestinal absorption of calcium is reduced which results in elevated PTH levels and subsequently parathyroid gland hyperplasia [26]. In CKD stages 3–4, calcium and phosphorus levels are usually in the physiologic range [27]. The majority of patients with CKD have low vitamin D [28]. The KDOQI guidelines recommend correction with vitamin D especially in stages 3 and 4 as these low levels may trigger the development of hyperparathyroidism. Supplementation of vitamin D with either ergocalciferol or cholecalciferol increases the level of 25HD and 1,25 (OH)D2 and may suppress but not necessarily normalize PTH in stages 3–4. In Stage 5, supplementation with vitamin D is generally ineffective in suppressing PTH levels.

The deficiency of endogenous calcitriol production is often treated with biologically active VDR agonist such as calcitriol, paricalcitol, alfacalcidol (not approved for use in the United States), and doxercalciferol. These active sterols increase the absorption of calcium and phosphorus from the intestines and in turn decrease the synthesis of PTH in a dose dependent manner regardless of the stage of CKD. Dialysis patients have impaired uptake and metabolism of 25HD. Calcitriol not only replete the levels of 1,25-D but also increases the uptake of 25HD [29]. However, These drugs are limited by the development of hypercalcemia and hyperphosphatemia, especially at higher doses and have a narrow therapeutic index [30]. The currently available synthetic analogs reduce PTH to a similar extent although paricalcitol achieves this reduction sooner than the other drugs [31]. In addition, paricalcitol showed significant and sustained control of PTH, with fewer episodes of hypercalcemia [32].

Intravenous calcitriol has been used since the late 1980s as an alternative therapy to either oral calcitriol or parathyroidectomy in adult dialysis patients with SHPT. Long term treatment showed reductions in PTH as well as alkaline phosphatase [33]. In addition, lowering PTH was also shown to be cardioprotective [34]. Widespread use of intravenous calcitriol has resulted in fewer parathyroidectomies [35].

Low vitamin D and 1,25 (OH)D2 levels correlate with increased cardiovascular disease and deaths, while the use of VDR agonist therapy may be cardioprotective. There are few prospective studies evaluating the effects of VDR agonist on survival. Previous meta-analysis showed Vitamin D supplementation was beneficial in lowering cardiovascular and all-cause mortality in patients with CKD [36]. Paricalcitriol has a greater survival advantage over calcitriol [36]. Contrary to the above, current evidence on Vitamin D supplementation does not support a benefit in survival or cardiovascular mortality in patients with CKD [37].

Continuous use of a VDR agonist results in lowering PTH, preserving bone mass, and lowering markers of bone remodeling such as bone specific alkaline phosphatase and osteocalcin [38, 39]. There is a lack of data on the effectiveness of the interrupted use of VDR agonist. Continuous therapy is recommended in order to maintain PTH suppression.

Therapy and goals for optimal PTH suppression need to be individualized. Occurrence of hypercalcemia due to VDR agonist may suggest

the development of adynamic bone, a form of renal osteodystrophy characterized by a low bone turnover state [40]. VDR agonists can be used to achieve PTH suppression while ensuring that hypercalcemia and hyperphosphatemia do not occur.

Calcium-Sensing Receptor Agonist: Cinacalcet

The calcium-sensing receptor (CaSR) is a G protein-coupled receptor located on the parathyroid chief cell membrane and represents the pivotal mechanism regulating PTH secretion. This receptor was initially cloned from bovine parathyroid cells and described by Brown et al. [41]. Activation of this receptor by an increase in extracellular calcium, the endogenous ligand, decreases PTH secretion [42]. The lack of a drug capable of directly altering PTH secretion without affecting serum calcium levels made the CaSR a high priority molecular target [43].

Ligands that simulate or potentiate the effects of extracellular calcium at the CaSR have been termed calcimimetics. There are two mechanistically distinct types. Type I calcimimetics are inorganic and organic polycations that act as agonists. Type II calcimimetics are L-amino acids and phenylalkamines that function as allosteric activators [44]. These type II drugs interact with membrane-spanning portions of the CaSR and induce conformational change in the receptor. This conformational change lowers the threshold for CaSR activation by plasma calcium, thereby reducing PTH secretion without a change in the serum calcium level [45].

The first-generation calcimimetic drug candidate was NPS R-568, a phenylalkamine type II compound. NPS R-568 was shown to selectively activate the parathyroid CaSR and inhibit PTH secretion both in vitro and in vivo [46]. However this compound demonstrated a variable pharmacokinetic and molecular profile [47]. This prompted the development of cinacalcet HCl, or (αR)-(−)-α-methyl-*N*-[3-[3-[trifluoromethylphenyl] propyl]-1-napthalenemethanamine hydrochloride, a second-generation analog of NPS R-568 that possesses the same safety and efficacy with improved bioavailability.

Cinacalcet (Sensipar, Amgen, Thousand Oaks, CA) has been approved by the FDA for use in the US since 2004. Its indications include (1) treatment of SHPT in adult patients on dialysis for chronic kidney disease, (2) hypercalcemia in patients with parathyroid carcinoma, and (3) severe hypercalcemia in patients with primary HPT.

In SHPT, cinacalcet treatment results in a decrease in FGF23 levels and the effect on FGF23 is independent of the changes in PTH levels [48]. Orally administered cinacalcet has been shown to reduce PTH and this effect can be maintained long term [49]. In CKD patients not on dialysis, cinacalcet decreases the levels of PTH but can cause hypocalcemia, hyperphosphatemia, and hypercalciuria. Therefore close monitoring of these laboratory values is required [50, 51].

Long-term administration of cinacalcet is associated with reduced progression of abdominal aortic calcification and uremic arteriolopathy [52]. Appropriate calcium and phosphorus levels may be achieved and together these changes reduce the rates of cardiovascular events and mortality in patients on hemodialysis [52, 53]. Cinacalcet did not reduce the risk of death or cardiovascular morbidity in those individuals on hemodialysis with moderate to severe hyperparathyroidism [54]. Nevertheless, addition of cinacalcet to standard therapy in adults with EGFR < 15 % (Stage 5) disease who were on dialysis, helped prevent surgical parathyroidectomy.

Cinacalcet resulted in a higher incidence of hypocalcemia. The data is robust for individuals with EGFR < 15 but sparse for those with EGFR between 15 and 60 ml/min/1.73 m^2 and kidney transplant recipients [55]. Cinacalcet does not reduce the rate of clinical fractures in patients on hemodialysis [56].

Combination Therapy

Low-dose cinacalcet plus calcitriol is more effective than calcitriol alone for the treatment of moderate and severe SHPT in chronic dialysis patients. Combination therapy resulted in fewer episodes of hyperphosphatemia and hypercalcemia [57]. When combined with VDR agonist, cinacalcet has been shown to reduce the parathyroid gland volume [58].

In head-to-head trial with a VDR agonist, cinacalcet was shown to be inferior to paricalcitol in suppressing bone turnover markers [59]. In adult patients on hemodialysis, intravenous paricalcitol was found to be more cost-effective than cinacalcet plus low dose vitamin D [60, 61].

Primary Hyperparathyroidism

A growing body of evidence exists to support the efficacy of cinacalcet in lowering plasma PTH and serum calcium levels in patients with PHPT [62, 63]. A phase 3 multi-center trial demonstrated that cinacalcet resulted in a significant plasma PTH reduction and serum calcium normalization compared to placebo [64]. Cinacalcet is effective and durable for multiple years for PHPT patients with varying degrees of disease severity [65]. In patients with PHPT and nephrolithiasis, the addition of cinacalcet to standard therapy and dietary measures led to a significant reduction in both the number and size of renal stones [66]. However, bone mineral density does not improve with cinacalcet therapy [67].

Cincalcet has also been shown to correct hypercalcemia and hyperparathyroidism in kidney transplant recipients [68].

Recent data have emerged to indicate that patients with mild, asymptomatic PHPT who do not meet surgical criteria for parathyroidectomy experience more effective biochemical control with cinacalcet compared to patients with surgical criteria. Patients without surgery criteria are more likely to reach normocalcemia at the end of the initiation phase, they maintain significantly lower serum calcium levels throughout treatment, and they experience stronger reductions in PTH level when compared to patients with surgical criteria [69]. This represents an active area of investigation, as neither the FDA nor the European Medical Agency currently approves cinacalcet for the treatment of PHPT with surgical criteria.

Surgical Intervention

Parathyroidectomy for SHPT is generally considered if the serum PTH levels are >1000 pg/ml with associated hypercalcemia, the volume of at least one hyperplastic gland is >500 mm^3 or SHPT is refractory to treatment.

Patients undergoing parathyroidectomy achieved the target KDOQI ranges 14–43 % of the time for calcium and 65–76 % for phosphate. However, most patients had a PTH below target [70]. Several smaller studies have looked at the survival benefit of parathyroidectomy versus medical treatment and have shown better cardiovascular and all-cause mortality with surgical intervention [71, 72]. There is ongoing debate about the preferred method of surgery; subtotal parathyroidectomy versus total parathyroidectomy with auto transplantation [73]. Currently total parathyroidectomy with or without autotransplantation is considered safe in patients with uncontrolled SHPT.

Summary

In this chapter, we have reviewed the etiology and treatment of secondary hyperparathyroidism. Secondary hyperparathyroidism is characterized by elevated PTH levels for an appropriate stimulus of hypocalcemia. In chronic kidney disease, the elevations in PTH fail to maintain calcium and phosphorus homeostasis. Current treatment options aimed at maintaining the phosphate balance and prevention of hyperphosphatemia. The new KDIGO guidelines do not recommend a specific target range for PTH, calcium, or phosphorus but rather individualize targets based on renal dysfuntion.

Society Guidelines As reviewed above.

Best Practices: N/A

Expert Opinion

Early diagnosis and treatment of SHPT is key. Dietary phosphate restriction and vitamin D supplementation is an effective treatment for CKD patients who are not on dialysis.

Vitamin D analogs and calcimimetics have shown to be effective in lowering PTH levels and can be used alone or in combination. Cost of these treatments can be prohibitive. Regular laboratory evaluations are needed. For SHPT that is refractory to medical treatment, parathyroidectomy remains a viable option.

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Tertiary Hyperparathyroidism

8

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Contents

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Introduction

Tertiary hyperparathyroidism is a state of parathyroid hormone (PTH) excess occurring during PTH secretion due to secondary hyperparathyroidism transitions from compensatory to autonomous. Clinically, this transition is marked by the development of hypercalcemia, with its associated symptoms and signs. It is most commonly observed in patients with renal failure who undergo a renal transplant in the setting of preexisting parathyroid autonomy. However, it can also be seen in patients with end-stage renal disease on dialysis as their longstanding secondary hyperparathyroidism progresses to an autonomous state. Advanced disease may result in severe hypercalcemia, along with complications not seen in hypercalcemia resulting from primary hyperparathyroidism, such as calciphylaxis. Because PTH secretion is autonomous, surgical treatment is usually required to normalize calcium and PTH levels. However, some patients may respond to treatment of the underlying cause of secondary hyperparathyroidism (e.g., renal failure or vitamin D deficiency), while in other cases therapy with cinacalcet may be effective.

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Historical Background

What we now recognize as tertiary hyperparathyroidism was first described in 1956 [1]. Davies described two patients with steatorrhea and hypercalcemia. The first patient had the waddling gait and pelvic pain associated with vitamin D deficiency, but her calcium levels were elevated, and X-rays of her spine showed the rugger-jersey spine changes typically associated with hyperparathyroidism. Her symptoms resolved with high-dose vitamin D therapy. The second patient presented with significant hypercalcemia and radiologic evidence of both osteomalacia and hyperparathyroidism. She was thought to have a parathyroid adenoma, and had a transient improvement in her calcium levels following the resection of the largest of the three parathyroid glands that were found at surgery. However, her hypercalcemia soon recurred, and a second surgery revealed a large parathyroid adenoma. She developed tetany postoperatively, but subsequently did well both clinically and radiologically. Davies noted that these two cases had findings similar to those seen in renal osteodystrophy. In his summary, he concludes with this insightful observation:

> … in some cases of steatorrhea a parathyroid hyperplasia occurs which is reversible with vitamin D treatment. In other cases, however, presumably of longer duration, one or more adenomata will develop. Treatment by operation will then be required, as in primary hyperparathyroidism.

Davies' two cases, one treated medically and the other surgically, is an early description of a clinical problem that is with us still: Which patients with tertiary hyperparathyroidism require surgery, and which can be observed or managed medically?

While Davies first described the process of prolonged secondary hyperparathyroidism developing into what he called primary hyperparathyroidism, it was St. Goar who 7 years later described this clinical presentation as "tertiary hyperparathyroidism" [2]. In his discussion of a case of a woman with renal disease who eventually developed hypercalcemia, St. Goar observed:

> By strict definition, secondary hyperparathyroidism is regarded as a compensatory mechanism functioning only to bring a low serum calcium up to or toward normal… When hypercalcemia occurs it no longer seems entirely accurate to use the term "secondary hyperparathyroidism"… likewise, the term "primary" hyperparathyroidism is unsatisfactory because of the background of underlying renal disease… Perhaps we should call this state "tertiary" hyperparathyroidism, since it develops on a background of "secondary" hyperparathyroidism.

St. Goar concludes by stating, "This is obviously no more than a problem in semantics, but it has contributed to the confusion of our understanding of the pathophysiology involved." This statement about tertiary hyperparathyroidism is as true today as it was when he made it more than 50 years ago.

Today, most cases of tertiary hyperparathyroidism occur in the setting of renal transplantation. The first kidney transplant was performed in 1960, and the first reported case of tertiary hyperparathyroidism following transplantation was 4 years later [3]. In that case, a young man with renal failure received a kidney transplant. At the time of his transplant, his serum calcium ranged from 8.0 to 10.0 mg/dL. Eight weeks later, his calcium rose to as high as 13.6 mg/dL. He subsequently underwent the removal of 3½ enlarged parathyroid glands with return of his serum calcium to the high normal range (~10 mg/dL). The authors correctly concluded "such cases of significant hypercalcemia may be seen more often as a consequence of the surge of interest in renal transplantation."

Causes of Tertiary Hyperparathyroidism

Any cause of longstanding secondary hyperparathyroidism has the potential to develop into tertiary hyperparathyroidism [4]. The most common of these is chronic kidney disease. In this setting multiple mechanisms combine to elevate PTH levels (see Chap. 2):

- As GFR levels fall, calcium reabsorption is impaired, resulting in hypocalcemia and increased PTH secretion.

- Rising phosphate levels increase PTH levels both directly, and indirectly by leading to worsening hypocalcemia.
- Normally, 1,25-dihydroxyvitamin D inhibits PTH synthesis and secretion. In chronic kidney disease, falling levels of 1,25-dihydroxyvitamin D in chronic kidney disease lead to increased PTH levels.
- FGF-23 normally acts on the parathyroid gland to reduce PTH levels. However, in the setting of chronic kidney disease, parathyroid tissue develops resistance to FGF-23, in spite of increased serum FGF-23 levels [5].
- Possible reductions in both calcium-sensing and vitamin D receptors on PTH secreting cells [6].

Over time, the continuous stimulation of parathyroid tissue causes parathyroid cell hyperplasia and the development of autonomous PTH secretion. Clinically, this transition from compensatory to autonomous PTH secretion results in calcium levels moving from low-normal, through the normal range, and eventually to hypercalcemia. Once hypercalcemia develops, the diagnosis of tertiary hyperparathyroidism can be made.

While tertiary hyperparathyroidism may develop in patients with longstanding renal failure, it is more commonly found in renal transplant patients who had significant secondary hyperparathyroidism at the time of their surgeries [7]. These patients are thought to develop some degree of parathyroid autonomy prior to transplant, but presumably not enough to result in hypercalcemia in the setting of renal calcium wasting and reduced calcium absorption from the gastrointestinal tract (due to low calcitriol levels). Following transplantation, and the return of normal renal and gastrointestinal calcium metabolism, the presence of autonomous PTH secretion now puts these patients at risk for the development of posttransplant hypercalcemia. The contribution of prolonged secondary hyperparathyroidism to the development of tertiary disease is supported by data showing that the duration of dialysis prior to transplant is a risk factor for posttransplant hyperparathyroidism [8]. Similarly, patients who received living donor transplants, and presumably were on dialysis for a shorter period of time, had lower PTH levels postoperatively than patients whose transplants had come from deceased donors [9].

Longstanding vitamin D deficiency (of any etiology) may result in secondary hyperparathyroidism. In patients with severe disease, this may progress to tertiary hyperparathyroidism with autonomous PTH secretion. However, the low levels of vitamin D may mask the calcemic effects of this marked hyperparathyroidism. Vitamin D replacement in this setting may convert secondary hyperparathyroidism into tertiary disease necessitating parathyroidectomy. This pathophysiology has been observed in patients with vitamin D deficiency from celiac sprue, treatment with phenytoin, and gastrectomy [10–12].

A group of disorders often referred to as vitamin D resistant rickets can, in some clinical settings, result in tertiary hyperparathyroidism. In spite of the name, the clinical manifestations of rickets in these patients are not mediated by vitamin D deficiency, but instead by urinary phosphate wasting. The common mechanism of this phosphaturia is elevated levels of FGF-23, an inhibitor of renal phosphate reabsorption. Multiple forms of hereditary phosphaturic rickets have been described. In *X-linked hypophosphatemic rickets,* there is a defect in the protease PHEX that indirectly results in elevated FGF-23 levels [13]. In both the *autosomal dominant* form of hypophosphatemic rickets and in *oncogenic osteomalacia*, an activating mutation directly increases FGF-23 levels. In untreated forms of these disorders, phosphate levels are low, but calcium levels are typically normal. Treatment with phosphate has the unintended effect of reducing serum calcium levels, resulting in increased PTH secretion. Chronically, this treatment-induced form of secondary hyperparathyroidism may develop into tertiary disease. The development of tertiary hyperparathyroidism has been reported in phosphate-treated patients with various forms of hypophosphatemic rickets [14–17], and oncogenic osteomalacia [18].

Pseudohypoparathyroidism type 1b has also been associated with tertiary hyperparathyroidism [19]. In this disorder, the loss of $G_s\alpha$ expression in

the renal tubule leads to PTH resistance. This results in urinary calcium wasting and reduced levels of 1,25-dihydroxyvitamin D, with subsequent secondary hyperparathyroidism. As in the disorders described above, these patients are at risk for the progression of their secondary hyperparathyroidism to tertiary disease with the development of hypercalcemia. Interestingly, the elevated levels of PTH may result in hyperparathyroid bone disease in these patients, since the renal tubular $G_s\alpha$ mutation is not present in skeletal tissue.

Pathology

Parathyroid gland pathology in tertiary hyperparathyroidism may take a variety of forms. Multiglandular parathyroid hyperplasia is seen in virtually all patients. Some patients will also have multiglandular adenomas that are the result of clonal proliferation [20]. It is reasonable to consider the hyperplasia to be a consequence of longstanding secondary hyperparathyroidism, with the adenomas being the etiology of the autonomous PTH production characteristic of tertiary hyperparathyroidism. Duan endorses the term "nodular parathyroid disease" to describe these findings. Grzela and colleagues reviewed the pathology of 19 patients with tertiary hyperparathyroidism [6]. They examined 64 glands and found 58 with hyperplasia, two with adenomas, and four with normal pathology. There have been a very small number of patients reported with parathyroid carcinoma in the setting of tertiary hyperparathyroidism [21]. However, it is not clear if there is a causal relationship between the preexisting secondary or tertiary hyperparathyroidism and the rare development of parathyroid carcinomas.

Clinical Presentation

Patients with tertiary hyperparathyroidism have many of the same symptoms and clinical findings as patients with longstanding hypercalcemia of other etiologies. These include fatigue, altered mental status, pruritus, bone pain, fractures, peptic ulcer disease, pancreatitis, nephrolithiasis, and nephrocalcinosis. However, other manifestations of hypercalcemia, including calciphylaxis and brown tumors of the jaw may develop in patients with tertiary (or longstanding secondary) hyperparathyroidism.

Calciphylaxis is a rare, devastating, and poorly understood disorder that has been associated with multiple medical conditions, including patients with end-stage renal disease on dialysis and tertiary hyperparathyroidism [22]. Its pathogenesis remains unclear. On histology, ischemic regions are seen in the dermis and subcutaneous fat along with calcification in the walls of medium-sized blood vessels [23]. Patients present with painful, poorly healing skin lesions that are prone to ulceration and infection. These lesions may occur after minor trauma or subcutaneous injections. Calciphylaxis is often attributed to elevations in the calcium-phosphate product, but that relationship remains unproven [22, 23]. Furthermore, it is also seen in patients with other disorders who have normal calcium and phosphate levels. Nevertheless, in patients with tertiary hyperparathyroidism and calciphylaxis, treatment is centered on reducing calcium and PTH levels (see section "surgical treatment," below).

Brown tumors (osteoclastomas) are benign, but locally destructive lesions that can develop in patients with persistent hyperparathyroidism of any etiology. They generally develop in cortical bone. The early diagnosis and treatment of primary hyperparathyroidism now makes them quite rare in that clinical setting. However, they have been reported in patients with tertiary hyperparathyroidism [24, 25]. These lesions will often regress following parathyroidectomy. In some cases either systemic or intralesional steroid therapy has been used following surgery. Brachydactyly, another now rare abnormality associated with severe hyperparathyroidism, has also been reported in tertiary disease [26]. These patients present clinically with foreshortened distal phalanges, which on X-ray are associated with osteolysis of the distal phalangeal tufts.

Surgical Treatment

The prevalence of hypercalcemia following renal transplant has been reported to decline from 31 % to 12 % over the first year [27]. The prevalence of parathyroidectomy in several recent series of posttransplant patients ranges from 0.6 % to 5.6 % [7, 9, 28]. Thus, most patients with tertiary hyperparathyroidism do not progress to parathyroidectomy. There are currently no well-accepted guidelines for parathyroidectomy in patients with tertiary hyperparathyroidism. (This is in contrast to primary hyperparathyroidism, where well-established criteria exist [29]). To address this issue, several groups have proposed criteria for parathyroidectomy in patients with renal transplantation [7, 23, 30–32]. These recommendations are summarized in Table 8.1. Most of these indications are based on clinical experience rather than controlled studies, and outcomes data from randomized controlled trials are not available.

The timing of the treatment of posttransplant tertiary hyperparathyroidism is controversial. PTH levels fall most acutely during the 3 months following transplant, and may continue to fall more slowly for up to a year [33]. However, there is some evidence that prolonged hyperparathyroidism and hypercalcemia may have an adverse effect on allograft function [32, 34]. Therefore, in the setting of mild to moderate posttransplant elevations in serum calcium, most authors recommend waiting 6–12 months before making the diagnosis of tertiary hyperparathyroidism and proceeding with parathyroidectomy [31].

Table 8.1 Indications for parathyroidectomy in patients with posttransplant tertiary hyperparathyroidism

Severe hypercalcemia (>11.5 mg/dL)
Calciphylaxis
Persistent hypercalcemia more than 3–12 months post transplant
Persistent hypercalciuria or phosphate wasting
Fractures, bone pain, or rapid bone loss
Nephrocalcinosis
Pruritis
PTH gland size > 500 mg (by ultrasound)
Severe fatigue
Peptic ulcer disease
Mental status changes
Nephrolithiasis
Severe myopathy

Just as there is no widespread agreement on patient selection or the timing of parathyroidectomy, consensus on the specific type of operation is also lacking. Total parathyroidectomy with autotransplantation of a small amount of parathyroid tissue into the forearm was the operation of choice for decades. The advantages of this approach include a high degree of success in resolving hyperparathyroidism and an easily accessible parathyroid remnant should hyperparathyroidism recur. However, this operation can be complicated by the development of hypoparathyroidism and hypocalcemia [35], along with variations in the viability of the transplanted tissue. At the other end of this surgical spectrum is a subtotal or limited parathyroidectomy. This approach is successful in the primary goal of treating hypercalcemia, but in one report was associated with a fivefold increase in persistent or recurrent hyperparathyroidism [36]. More recently, near-total (3½ gland) parathyroidectomy has been gaining acceptance as the procedure of choice in patients who require surgery for tertiary hyperparathyroidism [7, 31, 37, 38]. Although evidence remains limited, this "middle ground" attempts to balance the need for a major reduction in parathyroid tissue mass with the goal of avoiding postoperative complications including permanent hypoparathyroidism [30].

Medical Treatment

The approval of the calcium-sensitizing agent cinacalcet in the United States in 2004 provided a medical option for the treatment of patients with hyperparathyroidism as a result of end-stage renal disease. Cinacalcet acts as calcium receptor agonist, resulting in decreased PTH secretion. The most common use of cinacalcet in end-stage renal disease is in the treatment of secondary hyperparathyroidism, with

the goal of reducing elevated PTH levels and preventing the development of tertiary hyperparathyroidism. However, cinacalcet has also been used in the treatment of patients with tertiary disease. Two studies published in 2005 [39, 40] reported the effects of cinacalcet on patients with tertiary hyperparathyroidism. In both studies, calcium levels fell into the normal range. In Serra's trial of 11 patients studied for 10 weeks, PTH levels decreased by 21 %, phosphate levels rose but stayed in the normal range, and renal function remained stable. In Kruse's study of 14 patients treated for 3 months, calcium levels normalized in 12, but changes in PTH and phosphate levels were not statistically significant. Renal function slightly declined from 1.58 mg/dL at baseline to 1.67 mg/dL after 3 months.

Yang retrospectively compared patients with tertiary hyperparathyroidism who were either observed, treated with cinacalcet, or who underwent parathyroidectomy [32]. Not surprisingly, the patients treated with parathyroidectomy had higher calcium levels and a shorter time before surgery than the patients who were started on cinacalcet. Parathyroidectomy reduced calcium levels compared to observed patients, but the differences were smaller when parathyroidectomy and cinacalcet treatment were compared. Renal function remained stable in all three groups. Somnay retrospectively examined the effects of parathyroidectomy on patients who were receiving cinacalcet at the time of their surgeries [41]. Patients who were treated with cinacalcet had a higher incidence of hungry bone syndrome compared to untreated patients undergoing parathyroidectomy, but cure rates were equivalent and no other cinacalcet-related complications were reported. The authors note that the increased incidence of hungry bone syndrome in the cinacalcet-treated patients may have been a consequence of prolonged duration of their tertiary hyperparathyroidism prior to surgery. Overall, cinacalcet treatment appears to be a reasonable choice in patients with mild tertiary hyperparathyroidism who do not wish to proceed with parathyroidectomy or who are not good operative candidates.

Summary

Tertiary hyperparathyroidism occurs in the setting of longstanding secondary hyperparathyroidism and represents the development of autonomous PTH secretion after prolonged parathyroid gland stimulation. While any cause of secondary hyperparathyroidism may progress to tertiary disease, it is most commonly seen in patients who have had renal transplants. Calcium levels in this group of patients typically fall over the first year following transplantation. However, persistent hypercalcemia and the development of related symptoms and signs (Table 8.1) are indications for parathyroidectomy. Near-total parathyroidectomy appears to be the procedure of choice, balancing the risks of postoperative hypoparathyroidism and disease recurrence. Cinacalcet therapy is another treatment option for patients who may not be candidates for parathyroidectomy.

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Expert Opinion

The diagnosis and treatment of tertiary hyperparathyroidism remain areas of active research. However, emphasis on the management of secondary hyperparathyroidism in the setting of end-stage renal disease is critically important in preventing the development of tertiary disease. Advances in both medical and surgical therapy have the potential to reduce the incidence and sequela of this disorder.

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Part IV

Medical Therapy for Parathyroid Disease (Indications and Pharmacotherapy)

Hypercalcemia

9

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Contents

Introduction

Hypercalcemia is a common medical problem in clinical practice. Many patients are asymptomatic at presentation [1]. Mechanisms of hypercalcemia include increased bone resorption, increased gastrointestinal absorption of calcium and/or increased renal calcium reabsorption. Hypercalcemia can be classified into parathyroid hormone (PTH)-dependent and PTH-independent causes [2]. Primary hyperparathyroidism (PHPT) and malignancy-associated hypercalcemia (MAHC) represent the most common etiologies of hypercalcemia and comprise approximately 80–90 % of the causes of hypercalcemia [3]. In this chapter we will discuss the etiology, clinical manifestations, diagnostic approach, and management of hypercalcemia (Table 9.1).

Etiology

PTH-Dependent Hypercalcemia

Primary Hyperparathyroidism (PHPT)

PHPT is the leading cause of parathyroid hormone (PTH)-dependent hypercalcemia. The reported incidence is approximately 66/100,000 women and 25/100,000 in men [1]. This condition is usually identified at an asymptomatic stage due to routine measurements of serum calcium.

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Table 9.1 Causes of hypercalcemia[a]

PTH-dependent hypercalcemia
Primary hyperparathyroidism
Familial hypocalciuric hypercalcemia
Tertiary hyperparathyroidism
Ectopic PTH production by a tumor
PTH-independent hypercalcemia
Increased bone resorption
Humoral hypercalcemia of malignancy (HHM)
Local osteolytic metastasis
Hyperthyroidism
Vitamin A intoxication
Immobilization
Increased calcium absorption
Malignancy-induced 1,25 dihydroxyvitamin D
Granulomatous diseases
Vitamin D intoxication
Milk alkali syndrome
Parenteral nutrition
Drugs: thiazides, lithium, theophylline toxicity, PTH analogues
Miscellaneous causes: Adrenal insufficiency, Pheochromocytoma, Rhabdomylolysis, Jansen's Metaphyseal Chondrodysplasia, Congenital Lactose Deficiency, William's Syndrome

[a]Modified from Pallan et al. BMJ [94]

In countries without routine serum calcium measurements PHPT is often symptomatic at presentation [4].

PTH is a key regulator of serum calcium [5]. The synthesis and secretion of PTH from the parathyroid chief cells increases upon detection of low circulating calcium levels by the calcium sensing receptor (CaSR) in the parathyroid chief cells. PTH binds to PTH receptors (PTH1R), the G protein coupled receptors on the cellular surface of bone osteoblasts and osteocytes [6]. This leads to increases in the expression of RANKL (ligand for the receptor activator of NFkB) by the osteoblast which in turn binds to its receptor RANK on preosteoclasts and osteoclasts and increases the formation, function, and survival of osteoclasts enabling increased bone resorption and the mobilization of calcium from skeletal reserves [6]. PTH may also mobilize the release of calcium from the bone surface without increasing bone resorption; however, this possible mechanism requires further study [5].

In the kidney PTH binds to PTH1R receptors on proximal and distal tubule cells and increases renal calcium reabsorption within minutes. The cortical thick ascending limb (CTAL) of Henle's loop and the distal convoluted tubule (DCT) are the major sites of action for PTH and 1,25 dihydroxyvitamin D (1,25(OH)2 vit. D) [5–7]. PTH increases the renal production of 1,25(OH)2 vit. D by stimulating the synthesis of 1-alpha hydroxylase, allowing for increased absorption of calcium in the gut. 1,25(OH)2 vitamin D also increases RANKL expression on osteoblasts and thus increases bone resorption and the release of calcium from the skeleton [7].

In PHPT abnormal parathyroid tissue continues to synthesize and secrete PTH inappropriately in the presence of hypercalcemia . The precise pathophysiology for the development of this condition in sporadic cases is not known. It appears that the calcium set point is higher than normal. This set point is the calcium level where half-maximal suppression of PTH occurs. In sporadic PHPT this set point appears to be altered by 15–30 % permitting ongoing PTH secretion in the presence of high serum calcium [5]. In cases of PHPT specific gene abnormalities lead to failure of tumor suppressor activity, over expression of PTH precursor proteins, alterations in the calcium sensor and failure of inhibitors of cell growth [7].

The majority of individuals with PHPT have a single parathyroid adenoma (80 %), while four gland hyperplasia is seen in only 10–15 % [7, 8]. The genetic conditions implicated are multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2 (MEN2), multiple endocrine neoplasia type 4 (MEN4), hyperparathyroidism-jaw tumor syndrome (HPT-JT), and isolated familial hyperparathyroidism [7, 8]. Parathyroid carcinoma is fortunately a rare cause of PHPT [7, 8].

PHPT may be familial or sporadic. Familial PHPT is inherited as an autosomal dominant trait and may be part of a syndrome. Sporadic PHPT may also be due to a germline mutation which is de novo and the patient may be the only known case in that specific family. It is also possible that family members with PHPT may not have been identified and may have had asymptomatic

disease or may have died before the condition developed. Sporadic parathyroid adenomas may be caused by a single gene mutation in a progenitor cell, leading to unregulated proliferation of parathyroid tissue. Chromosome 11 breakage and inversion leads to overexpression of a PTH promoter regulatory protein, cyclin D1. This rearrangement has been reported in 5 % of parathyroid adenomas. The cyclin D1 protein is overexpressed in 18–41 % of all parathyroid adenomas. Another implicated chromosome is chromosome 1p32-pter [7, 8]. Parathyroid adenomas are usually composed of parathyroid chief cells; however, oxyphil cell adenomas have been reported [9]. These lesions are more commonly seen in women post menopause.

Familial PHPT

The most common types of familial hyperparathyroidism are multiple endocrine neoplasia type 1 (MEN1) and type 2 (MEN2). MEN1 is associated with tumors of the parathyroids, pancreatic islets, and the anterior pituitary and is due to a germline mutation in the MEN 1 gene. This gene encodes menin a tumor suppressor [8]. This protein inhibits tumor formation in pancreatic, pituitary, and parathyroid tissues. Hyperparathyroidism has nearly 100 % penetrance in affected patients, and usually presents in the third decade [10].

MEN2 is due to mutations in the RET (rearranged during transfection) proto-oncogene which encodes a tyrosine kinase receptor and leads to the development of parathyroid tumors, medullary thyroid cancer, and pheochromocytoma [10]. MEN 3 is also due to RET mutations and is associated with medullary thyroid cancer, pheochromocytoma, and a marfanoid habitus. It is also associated with mucosal neuromas, medullated corneal fibers, and dysfunction of the autonomic ganglia in the bowel leading to megacolon and diverticulosis. Parathyroid tumors are rare in MEN 3 [10].

Patients with MEN4 have tumors in the parathyroids, anterior pituitary as well as gonads, adrenals and kidneys [10] and have mutations in the CDNK1B gene which encodes the cyclin-dependent kinase inhibitor CDK1 p27 kip1 [11]. To date, patients reported with MEN4 have had parathyroid adenomas and primary hyperparathyroidism, whereas expression of other endocrine tumor types has been variable. Cyclin-dependant kinase inhibitors (CDKIs) are cell cycle regulators which may become inactivated in endocrine neoplasias [11].

HPT-JT is associated with PHPT, jaw tumors, renal cysts, and renal hamartomas . Pancreatic adenocarcinoma, uterine and testicular tumors may also occur. Like MEN1, hyperparathyroidism is strongly expressed, occurring in 90 % of affected patients. However in HPT-JT the parathyroid tumors are usually single adenomas or carcinoma whereas in MEN 1 multiglandular disease is present [10]. In HPT-JT syndrome the HRPT2 gene is inactivated. This gene encodes a tumor suppressor parafibromin. When parafibromin is inactivated permissive tumor growth occurs [8].

The inheritance of MEN1, MEN2, MEN3, MEN4, HPT-JT, and isolated familial hyperparathyroidism are all autosomal dominant [7, 8, 11].

Parathyroid Carcinoma

Parathyroid carcinoma is an unusual cause of primary hyperparathyroidism. It may arise sporadically or may develop in abnormal parathyroid tissue such as parathyroid hyperplasia, adenoma, following neck irradiation, renal disease, or prolonged secondary hyperparathyroidism [12, 13]. These associations have not been consistently observed or reported and require further study. Familial parathyroid carcinoma does occur and is associated with HPT-JT syndrome in which there is an abnormal chromosome 1q31.2 and in isolated familial hyperparathyroidism [8, 13]. Like parathyroid adenomas, parathyroid carcinomas frequently demonstrate overexpression of cyclin D1. This overexpression of cyclin D1 has been reported in up to 91 % of these tumors [13]. Parathyroid carcinoma is rare and occurs in only 1–2 % of all PHPT [13].

The presentation of parathyroid carcinoma is similar to the presentation of PHPT; however, patients with carcinoma usually have severe hypercalcemia in comparison to individuals with benign parathyroid disease [12, 13]. In parathyroid

carcinoma significant elevations in PTH and calcium levels are present with serum calcium usually being higher than 3.5 mmol/L. The mean PTH elevation in one review was 10 times above the upper limit of normal [13]. This distinguishes carcinoma from benign parathyroid disease. The mean age for the presentation of parathyroid carcinoma is in the fifth decade. Parathyroid carcinoma occurs equally in males and females, whereas benign parathyroid disease occurs more commonly in females. Individuals with parathyroid carcinoma may present with a neck mass. Despite these clinical clues, parathyroid carcinoma is often diagnosed on surgical pathology [12, 13].

Familial Hypocalciuric Hypercalcemia

Familial hypercalcemic hypocalciuria (FHH) is a rare autosomal dominant disorder due to an inactivating mutation of the CaSR on the parathyroid cells and in the kidney tubules [14–18].

In this disorder, the PTH level may be increased due to decreased parathyroid cell sensitivity to the elevated serum calcium concentration. Approximately 5–10 % of patients have a minimal elevation of PTH [18]. The renal tubular calcium reabsorption is increased in association with impaired function of the CaSR in the kidney in addition to increased PTH secretion [15]. The loss of CaSR function enhances renal tubular reabsorption of magnesium [18]. Patients usually present during childhood and have a positive family history of hypercalcemia. Almost all patients have hypercalcemia; however, the degree of hypercalcemia is mild and the majority of patients are asymptomatic or have minimal symptoms only [19]. Calculating the calcium/creatinine (Ca/Cr) clearance ratio enables differentiation of FHH from PHPT [20]. In approximately 80 % of cases of FHH the Ca/Cr clearance ratio is less than 0.01. In the remaining patient population a higher calcium to creatinine clearance ratio can be seen up to 0.02 making it difficult to differentiate FHH from PHPT particularly in the presence of vitamin D insufficiency or renal insufficiency [18]. DNA sequencing of the CaSR gene with identification of an inactivating mutation enables confirmation of the diagnosis [20]. Parathyroidectomy will not normalize the elevated serum calcium in FHH; however, in the rare circumstances of a homozygous inactivating mutation of the CaSR gene, a condition known as neonatal severe hyperparathyroidism, immediate parathyroidectomy is the treatment of choice [21].

Tertiary Hyperparathyroidism

Autonomous PTH secretion associated with hypercalcemia in patients with chronic kidney disease is known as tertiary hyperparathyroidism [22]. Although the mechanisms of tertiary hyperparathyroidism are not well understood, many theories suggest prolonged stimulation of the parathyroid glands results in anatomic hyperplasia with autonomous function of the parathyroid glands [23]. The expression of the CaSR and vitamin D receptors (VDRs) in tertiary hyperparathyroidism is decreased leading to further increases in PTH secretion. This may result from continuous parathyroid stimulation in secondary hyperparathyroidism, followed by further development of polyclonal autonomy [24]. Parathyroidectomy is the treatment of choice to eliminate the adverse effects of hypercalcemia and hyperparathyroidism [25].

Ectopic Parathyroid Hormone

Ectopic PTH secreting tumors are extremely rare. A few published cases in the last two decades have reported ectopic PTH secreting tumors. PTH secretion from small cell lung cancers, ovarian cancers, and papillary thyroid cancers have been described. Clinically this is characterized by increased parathyroid hormone and serum calcium concentration in the absence of parathyroid adenoma or hyperplasia on radiologic images [26–28].

PTH-Independent Hypercalcemia

Malignancy-Associated Hypercalcemia

Malignancy-associated hypercalcemia (MAHC) is the most common cause of hypercalcemia in hospitalized patients. It accounts for approximately 90 % of inpatient hypercalcemia [2]. Hypercalcemia is usually evident clinically when the diagnosis of malignancy is made and may

predict poor prognosis; however, it is unlikely to be the initial presenting symptom of malignancy [29]. Men are at a higher risk for developing hypercalcemia in the setting of malignancy. Though in general most hypercalcemic patients are women [29, 30].

Four mechanisms are responsible for the increased serum calcium concentration seen in malignancy. These include increased parathyroid hormone-related peptide (PTHrP) production which is a mechanism for humoral hypercalcemia of malignancy (HHM), increased production of osteolytic factors, increased production of 1,25 dihydroxyvitamin D ($1,25(OH)_2$), and finally ectopic parathyroid hormone release by tumor cells [2]. Eradication of the tumors is the treatment of choice in MAHC [2].

Humoral Hypercalcemia of Malignancy

Excessive secretion of PTHrP is the most common mechanism of MAHC. It accounts for approximately 80 % of MAHC [2]. The majority of the patients have squamous cell carcinoma most commonly lung tumors. Other malignancies including bladder, renal, breast, and ovarian carcinoma may be associated with elevated PTHrP. It can also rarely be seen in hematological malignancies such as Non-Hodgkin lymphoma and leukemia [2].

PTHrP is a member of the PTH family, identified in 1987 in cancer patients with hypercalcemia [31]. PTHrP shares a similar sequence homology with PTH in the first 13 amino acids at the N terminus [32]. Secretion of PTHrP, activates osteoclast activity and suppresses osteoblast activity leading to the release of calcium from the skeleton [32]. PTHrP increases renal calcium reabsorption and decreases phosphate reabsorption in renal tubules resulting in hypercalcemia, hypocalciura, hypophosphatemia, and hyperphosphaturia [33]. In contrast to PTH, PTHrP does not increase the intestinal calcium reabsorption due to an inability to activate 1-α hydroxylase and hence 1,25(OH)2 vitamin D production [33]. This difference in the action of PTHrP in comparison to PTH relates to differences in the parathyroid hormone 1receptors (PTH1R) in comparison to PTH. In addition, PTHrP does not bind to the PTH2R which is present in the gastrointestinal tract (GIT) [34, 35]. The elevations in PTHrP seen in gynecologic tumors and in pheochromocytoma normalize with surgical removal of these tumors [36–38].

Local Osteolytic Metastasis

Local osteolytic metastasis contributes to hypercalcemia and account for approximately 20 % of malignancy-associated hypercalcemia in one large series [2]. Some solid tumor cells produce local PTHrP, this occurs in metastatic breast cancer to the bone with upregulation of RANKL expression in bone [39, 40]. In contrast, myeloma cells produce cytokines including interleukin-6 (IL-6), IL-3, IL-1, and macrophage inflammatory protein 1α (MIP1). These osteoclastogenic molecules increase RANKL expression and decrease the production of osteoprotegerin (OPG). The elevated RANKL/OPG ratio increases the osteoclast activity and bone resorption [41–43]. Other hematological malignancies may mimic multiple myeloma in increase calcium release from the skeleton [44].

Thyrotoxicosis

Hypercalcemia can be seen in hyperthyroidism. Thyroid hormone activates the RANKL/RANK system via increased expression of osteoclastic cytokines. This results in increased calcium concentration in the serum [2]. It is usually associated with increased levels of the circulating IL-6 [45]. Although calcium absorption decreases in the gut and calcium excretion increases through the kidney due to suppressed PTH, up to 50 % of hyperthyroid patients have elevated total or ionized calcium [46]. Most of these patients have mild elevation of calcium; severe hypercalcemia in hyperthyroid patients is rarely seen [2]. Correction of thyroid hormone level will restore the balance of osteoclast/osteoblast activity in the bone and normalize calcium and PTH levels in the blood [47].

Hypervitaminosis A

Vitamin A is a fat soluble vitamin which is stored in the liver. Hypercalcemia can be caused by vitamin A intoxication. The mechanism is not

well understood but may be due to direct stimulation of osteoclast bone resorption or stimulation of other cytokine expression [48]. The causes of hypervitaminosis A are related to high vitamin A intake as a supplement especially in chronic kidney disease or as a treatment of certain tumors or dermatological diseases by retinoic acid derivatives [49].

Immobilization

Prolonged immobilization can increase osteoclast activity and suppress osteoblast activity causing calcium release from the bone into the circulation. Hypercalciuria occurs as a result of increased bone remodeling [50]. Diseases associated with prolonged immobilization include spinal cord injury, stroke or multiple fractures and may present with hypercalcemia. Immobilized patients with Paget's disease may also present with hypercalcemia [2]. Both young adults and the elderly are at risk for increased calcium levels with prolonged immobilization [51]. In addition to bisphosphonate administration, early mobilization and adequate hydration will reduce the risk of hypercalcemia by suppressing bone resorption and increasing the urinary excretion of calcium [51, 52]. Denosumab can be used in hypercalcemic immobilized patients after partial or transient response to bisphosphonate [53].

Malignancy-Induced 1,25 Dihydroxyvitamin D

Overexpression of the enzyme 1-α hydroxylase by malignant cells or adjacent normal cells converts 25-hydroxyvitamin D into abnormally elevated $1,25(OH)_2$ vitamin D (calcitriol) level [2]. This leads to increased calcium absorption from the gut and results in hypercalcemia in the presence of suppressed PTH level, with normal phosphate level in the blood, absence of renal phosphate wasting and increased renal calcium excretion initially and decreased renal clearance over time as a result of dehydration [2]. Calcitriol also has a direct effect on RANKL/RANK system leading to increased osteoclast activity and bone resorption [2]. These pathophysiological abnormalities have been reported in all types of lymphoma, particularly Hodgkin lymphoma and more than 30 % of non-Hodgkin lymphoma [54]. This mechanism also has been described in patients with ovarian dysgerminomas [55] and chronic granulomatous diseases such as sarcoidosis.

Granulomatous Diseases

Similarly, granuloma cells continue to produce 1α hydroxylase which converts 25-hydroxyvitamin D to 1,25(OH)2 vitamin D. This occurs in spite of suppressed PTH, leading to increased intestinal calcium absorption, bone resorption, hypercalciuria, and hypercalcemia [2]. Elevated calcitriol and calcium concentration in anephric patients with sarcoidosis support the idea of granuloma cells as the synthetic source of 1,25-dihyroxyvitamin D in the systemic disease not only the kidney [56]. Nearly all known granulomatous diseases have been reported to cause hypercalcemia via this mechanism. In sarcoidosis, about 30 % of patients have hypercalciuria and 10 % have hypercalcemia during their life [57]. The risk of hypercalcemia is aggravated with prolonged exposure to sun light and eating a diet rich in vitamin D [57]. In tuberculosis, the prevalence of hypercalcemia varies from one country to another depending on dietary intake of calcium and vitamin D. If the calcium or vitamin D intake is inadequate the prevalence of hypercalcemia will be low, but if the intake is adequate or high the prevalence will be high [58].

The treatment of choice in granulomatous diseases is prednisone. Calcium level often starts to normalize after 2 days of starting steroid therapy [2, 57]. Treatment of the underlying cause with antituberculosis or antifungal agents or adequate hydration as well as a low vitamin D and calcium diet with avoidance of prolonged sunlight exposure will reduce and maintain calcium level in the normal reference range [2]. Antifungal treatment such as Ketoconazole can be used as a second line therapy if patients with sarcoidosis do not respond to steroid therapy [57], or have severe symptoms [59].

Hypervitaminosis D

Vitamin D is a fat soluble vitamin which is stored in the liver with excess vitamin D being stored in fat cells. High concentrations of vitamin D, inactive 25-hydroxyvitamin D, and the

active metabolite 1,25(OH)2 D, can cause hypercalcemia by increasing intestinal calcium absorption and calcium efflux from the bone [2]. Hypervitaminosis D may be a result of excess intake of any vitamin D preparation orally or topically [60]. Cases have been reported of excessive vitamin D fortification of milk [61]. A further etiology is via the endogenous production of calcitriol associated with lymphomas and granulomatous diseases, discussed previously. Prolonged exposure to sunlight will not lead to vitamin D intoxication as excess photoconverted previtamin D3 and vitamin D3 will form two inactive metabolites, lumisterol3 and tachysterol3, which maintain vitamin D levels within a normal range [62].

Cessation of calcitriol and adequate hydration are the best treatment for hypercalcemia secondary to calcitriol due to its short half-life. Hypercalcemia induced by 25-hydroxyvitamin D (Calcidiol) requires more aggressive treatment with a bisphosphonate as it persists over a longer time period [63].

Milk Alkali Syndrome

In the past, milk alkali syndrome was described in patients with peptic ulcer disease who were treated with an excessive amount of milk and sodium bicarbonate. Now, it is more common in patients who are taking excessive amounts of calcium carbonate [64]. High calcium supplement intake results in increased calcium concentrations that induce diuresis by activation of CaSRs in the ascending limb of the Loop of Henle and interferes with antidiuretic hormone (ADH) action in collecting duct. This will cause volume contraction and increase bicarbonate absorption in the renal tubule leading to an elevated pH concentration in the blood [64]. Metabolic alkalosis may worsen the hydration status and aggravate the calcium level [64]. High renal tubule calcium concentrations activate the CaSRs in the distal convoluted tubules leading to increases calcium reabsorption via the transient receptor potential vanilloid member 5 (TRVP5 channels [65]. The glomerular filtration rate (e-GFR) will be reduced as a direct effect of hypercalcemia on renal arterioles and volume contraction in the acute stage, and nephrocalcinosis and nephrolithiasis in the chronic stage [64]. Thiazide diuretics, non-steroids anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, or any drugs or medications that reduce glomerular filtration rate may increase the risk to develop this syndrome [66]. Milk Alkali syndrome is characterized by hypercalcemia, metabolic alkalosis, and renal impairment. Treatment includes cessation of the insulting drug and administrating adequate hydration [64].

Parenteral Nutrition

The exact mechanism of parenteral nutrition-induced hypercalcemia is not fully understood. Administration of total parenteral nutrition (TPN) has been associated with hypercalcemia, hypercalciuria, and osteomalacia [67]. Hypercalcemia may be caused by excess calcium in the TPN solutions or increased bone resorption by excess vitamin D [67, 68]. TPN containing contaminated casein hydrolysate with aluminum can cause low bone turnover resulting in unbalanced activity of markedly low osteoblasts and low or normal osteoclasts [68, 69].

Drugs

Thiazide

The direct action of thiazide on calcium reabsorption occurs in the distal convoluted tubule. Thiazides can also increase calcium reabsorption in the proximal tubule indirectly thorough the effect of volume depletion as a result of increased sodium and water excretion [70]. In general thiazides can cause mild hypercalcemia and hypocalciuria; however, severe hypercalcemia has been reported only in the setting of underlying primary hyperparathyroidism [71].

Lithium

Hypercalcemia may develop in patients on lithium therapy as a result of increased PTH secretion; this may occur more frequently in the elderly [72]. Lithium may unmask the presence of PHPT or lead to parathyroid adenoma formation or hyperplasia. Lithium has been postulated to inactivate the CaSR on parathyroid glands [2, 73]. Lithium also stimulates calcium reabsorption in the renal tubule and inhibits renal cyclic

AMP formation directly causing mild hypercalcemia, hypocalciuria, and low renal cyclic AMP [2, 74]. If a hypercalcemic patient cannot tolerate lithium withdrawal, close monitoring with active surveillance is a valuable treatment strategy. Cinacalcet, a calcimimetic agent, has been reported to normalize calcium levels in lithium-induced hypercalcemia [75]. Neck exploration and parathyroidectomy can be considered in symptomatic and severe hypercalcemia [76].

Theophylline Toxicity

Several reports have described hypercalcemia in the setting of theophylline toxicity. This occurs in a PTH-independent fashion. Normalization of calcium levels after propanolol administration to these patients suggests that an adrenergic effect may be responsible [77].

Parathyroid Hormone Analogues

Parathyroid hormone analogues are anabolic agents used for the treatment of osteoporosis. Two molecules are available: PTH (1-34) and PTH (184). Each is associated with mild and/or transient hypercalcemia which is rarely severe or persistent. Usually no intervention is required; however, dose reduction of PTH or even cessation of therapy may be required in severe cases [78].

Miscellaneous Causes

Other causes of hypercalcemia include adrenal insufficiency, pheochromocytoma, rhabdomyolysis, and rare genetic conditions such as Jansen's metaphyseal chondroplasia, congenital lactose deficiency, and William's syndrome.

Adrenal Insufficiency

Adrenal insufficiency is rarely complicated by hypercalcemia. This is described in the setting of acute adrenal crisis and responds to steroid replacement therapy. The etiology of hypercalcemia in this setting may be related to hemoconcentration or increased renal absorption of calcium at the level of the proximal tubules [79].

Pheochromocytoma

Pheochromocytoma is very rarely the cause of hypercalcemia. However, in patients with pheochromocytoma hypercalcemia may be the result of MEN2A (PHPT rather than pheochromocytoma is the true cause of hypercalcemia in this setting), or alternately the pheochromocytoma itself may produce PTHrP. VIPoma are also thought to produce PTHrP [80].

Rhabdomyolysis

Rhabdomyolysis may cause hypercalcemia upon release of calcium stored in muscle cells. With muscular injury these cells release calcium stores. Renal injury and secondary hyperparathyroidism may also contribute to hypercalcemia in this situation [81].

Jansen's Metaphyseal Chondrodysplasia

Jansen's Metaphyseal Chondroplasia is known to cause hypercalcemia with low or normal PTH levels. Here, hypercalcemia is the result of a mutation in the PTH-PTHrP receptor gene [82].

Congenital Lactose Deficiency

Congenital lactose deficiency is a rare recessive disorder presenting in infancy with nausea, vomiting, failure to thrive, and diarrhea. The exact mechanism for hypercalcemia in this population is unclear. It has been hypothesized that nonhydrolyzed lactose has a direct enhancing effect on calcium absorption on the ileum [83].

William's Syndrome

William's syndrome is a genetic disorder of chromosome 7 resulting in variable expression of craniofacial abnormalities, aortic stenosis, hypertension, hypercalcemia, diabetes, thyroid disorders, cognitive impairment, or short stature. The hypercalcemia in this condition is typically asymptomatic and mild and resolves in the first 5 years of life. The etiology is unknown. Proposed mechanisms include enzyme deficiencies which prevent normal vitamin D3 breakdown [84].

Clinical Manifestations of Hypercalcemia

The symptoms and signs of hypercalcemia depend on the duration and severity of the hypercalcemia [2, 85, 86].

In mild hypercalcemia (serum calcium < 2.88 mmol/L {<11.5 mg/dl}), patients are usually asymptomatic or have mild symptoms such as polyuria and polydipsia. Frequently, patients manifest symptoms such as weakness, nausea, anorexia, and constipation in moderate hypercalcemia (serum calcium 2.88–3.5 mmol/L {11.5–14 mg/dl}). Acute severe hypercalcemia (serum calcium >3.5 mmol/L {>14 mg/dl}) may be associated with dehydration, vomiting, abdominal pain, decreased concentration, stupor and/or coma. These symptoms may present not only in severe hypercalcemia but also in acute hypercalcemia with rapid rises in serum calcium and can occur at lower levels of hypercalcemia i.e. <3.5 mmol/L (14 mg/dl) [85, 86]. Polyuria results from the renal effects of hypercalcemia. Prerenal acute renal impairment and dehydration may develop, particularly if it is associated with nausea and vomiting. The incidence of nephrolithiasis is increased in patients with chronic hypercalcemia [2, 85, 86]. Nephrocalcinosis, calcium deposition in renal tubules, renal stones, dehydration, and renal arteriolar vasoconstriction can impair renal function leading to ESRD. Hypercalcemia also affects the gastrointestinal tract (pancreatitis) as well as the cornea (keratopathy) [85, 86]. Hypercalcemia decreases the tone of intestinal smooth muscles and skeletal muscles causing constipation and generalized muscle weakness respectively. Nausea, anorexia, and abdominal discomfort may occur [2]. Arrhythmias in association with shortened Q-T interval may be seen [2, 85]. The neurological symptoms of hypercalcemia range from mild fatigue, decrease cognitive function, anxiety, and depression to more severe symptoms including stupor, confusion, and coma [85, 86].

Diagnostic Approach to Hypercalcemia

The first step in the evaluation of hypercalcemia is to confirm the presence of an elevated calcium level and to ensure it is not a fictitious elevation due to increased albumin concentration. This may occur as up to 45 % of calcium binds to albumin. Similarly, hypoalbuminemia as commonly seen in the elderly may result in falsely low total calcium levels [4, 86].

Calculating corrected calcium enables confirmation of the existence of hypercalcemia [4, 87, 88].

$$\text{Corrected calcium}\left(\text{mmol / L}\right)=\text{serum calcium}+0.02\times\left(40-\text{serum albumin g / L}\right)$$

$$\text{Corrected calcium}\left(\text{mg / dl}\right)=\text{serum calcium}+0.8\times\left(4-\text{serum albumin gm / dl}\right)$$

Measuring the ionized calcium is of value in ensuring that paraproteins are not contributing to falsely elevated serum calcium.

Measuring PTH is the next step to differentiate between PTH-dependent hypercalcemia (primary and hypercalcemia, FHH, and lithium) and PTH-independent hypercalcemia (cancer, hypervitaminosis D or A, granulomatous diseases, and endocrine diseases e.g. thyrotoxicosis) [2, 4, 89, 90]. PTH values in PHPT are inappropriately normal or elevated. Ionized calcium has been shown to correlate with adenoma size, degree of PTH elevation and may be more sensitive than total calcium for detecting calcium elevation and disease severity than total calcium [91]. Low 25-OH vitamin D levels may mask PHPT by reducing the degree of hypercalcemia. Similarly low vitamin D may stimulate elevations in PTH. In PHPT, low levels of 25 (OH) vitamin D <20 ng/dl (50 nmol/L) exacerbate disease activity [92]. Urine calcium excretion is measured both to rule out FHH and to evaluate the risk of renal stone formation or nephrocalcinosis in chronic hypercalcemia. A urinary biochemical stone risk profile would be beneficial in this setting. Currently, this is recommended when hypercalciuria is present at >10 mmol/L or 400 mg/day [92].

In PTH-dependent hypercalcemia, a 24 h urine collection should be completed and calcium/creatinine ratio calculated to differentiate between primary hyperparathyroidism and FHH [4].

PTH-independent hypercalcemia requires further work up to identify the cause of hypercalcemia. MAHC is the most common cause of PTH-independent hypercalcemia and it is associated

with high PTHrP in the majority of cancers [2, 89, 90]. Further imaging studies such as CT scanning and biochemical studies such as tumor markers may be completed to confirm the presence and type of carcinoma. Many tumors cause mass effects or obvious symptoms and diagnosis is usually confirmed prior to the discovery of the hypercalcemia [2]. Serum immunoelectrophoresis and urine protein electrophoresis are helpful in confirming the presence of a myeloproliferative disorder. 1,25 dihyroxyvitamin D is elevated in lymphomas as well as in granulomatous diseases. A chest X-ray may be useful in the further evaluation of increased 1,25 (OH)2 D to assess for tumors, sarcoidosis or tuberculosis. Hypervitaminosis D is simply confirmed by measuring 25-OH D which is defined by vitamin D levels >375 mmol/L (>150 ng/ml) or elevated 1.25(OH)2 D levels. Urinary calcium/creatinine ratio is also useful. High urinary calcium excretion is associated with enhanced gastrointestinal absorption as well as increased bone remodeling; while low excretion can occur with the use of thiazide diuretics. In the absence of a clear cause of hypercalcemia further tests may be of value and include thyroid function tests, vitamin A level, lithium level, fasting cortisol level, or a 24 h urine collection for catecholamines and metanephrines [2, 4, 89, 90].

A careful history and physical examination is the best initial approach to determine the etiology of hypercalcemia. A detailed history includes assessing patient comorbidities, activities, and drugs which may contribute to the development of hypercalcemia.

Treatment of Severe Hypercalcemia

No acute management is required for patients with mild (serum calcium<2.88 mmol/L {<11.5 mg/dl}) or moderate (serum calcium 2.88–3.5 mmol/L {11.5–14 mg/dl}) hypercalcemia. These patients are encouraged to be active and drink fluids to maintain adequate hydration. Avoidance of a high calcium diet and any drugs known to cause hypercalcemia such as calcium supplements, calcitriol, thiazides, or lithium is encouraged. Treatment of the underlying cause will restore the calcium level to the normal range [93].

In PHPT the definite treatment of hypercalcemia is surgery. The cure rate for PHPT with surgery is 95–98 % [92, 94]. Current guidelines recommend surgery by an experienced parathyroid surgeon for those with symptoms or asymptomatic patients with hypercalcemia> 0.25 mmol/L above the upper limit of normal, patients younger than 50 years of age, evidence of osteoporosis or those suffering from renal stones or renal impairment [92]. Those who do not qualify for, or do not wish to undergo parathyroid surgery are followed with medical management for potential disease progression. Medical therapy of PHPT is not curative, but can provide skeletal protection and lower serum calcium [92, 94, 95]. In PHPT cinacalcet reduces serum calcium to normal levels in 75.8 % of patients and decreases serum calcium in 84.8 % of patients. Limitations to the use of cinacalcet include primarily the cost. The drug is well tolerated with side effects consisting of nausea, diarrhea, arthralgias, myalgias, and parasthesias [94–96]. Calcitonin is useful in lowering serum calcium acutely [97]. Denusomab requires further evaluation in this setting.

The most common cause of severe hypercalcemia (serum calcium>3.5 mmol/L {>14 mg/dl}) is MAHC and patients with acute PHPT may also present with severe hypercalcemia. The initial management approach in these patients or any patient with severely symptomatic hypercalcemia is hydration with isotonic saline fluid. The rate of infusion is guided by the patient's hydration status as well as the presence of underlying cardiac or renal disease. Restoration of intravascular volume increases urinary calcium excretion [90, 93]. Adding loop diuretics such as furosemide permits further urinary calcium excretion and protects against volume overload, especially in patients suffering from cardiovascular disease [90, 93].

Calcitonin reduces calcium levels by decreasing osteoclast bone resorption and increasing urinary calcium excretion [90, 93]. Calcitonin decreases the level of serum calcium rapidly within the first 6 h of introduction and is a valuable option in the first 2 days of treatment [90, 93].

Calcitonin is effective intravenously, at a dose of 4 iu/kg every 4–6 h. Calcitonin is a useful option in combination with other medications such as bisphosphonates [90, 93].

Bisphosphonates are the preferred drug for the treatment of hypercalcemia as they are potent and relatively safe in a well hydrated patient. Bisphosphonates inhibit osteoclast mediated bone resorption. The onset of action is within 2–3 days and the effect may last for weeks [98]. The risk of osteonecrosis of the jaw, profound hypocalcemia, and renal toxicity may increase with repeated use of bisphosphonates in the oncology patient population [90]. Zolendronic acid is superior to pamidronate as it is a more potent agent with a shorter infusion time [99]. Ibandronate is also a safe and effective alternative [100].

Denosumab, a fully human monoclonal antibody, inhibits osteoclast activity and decreases bone resorption by binding to a receptor activator of nuclear factor-kappa ligand (RANKL) and prevents RANKL and RANK interaction [90]. Denosumab may be considered in bisphosphonate hypercalcemia [101]. Denusomab reduces calcium levels in 64 % MAHC patients who have persistent hypercalcemia despite treatment with bisphosphonate within 10 days of administration [102]. Denosumab can be used safely without dose adjustment in CKD as it is not renally excreted. Profound hypocalcemia is more frequent in patients with vitamin D deficiency and renal impairment [103]. Replacement with vitamin D is required for vitamin D deficient patients prior to administration of denusomab and reduction of administrating dose is required for patients with malignancy and renal impairment [104].

Dialysis, either peritoneal or hemodialysis may be required in the treatment of hypercalcemia in patients for whom large volume of intravenous fluids are contraindicated e.g. CKD or heart failure [99].

Summary

Hypercalcemia requires a careful clinical and laboratory evaluation and is effectively treated with the therapeutic options available today.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion

Hypercalcemia should not be ignored. It should be confirmed by repeat laboratory testing. When severe, it will require acute intervention, usually medical. In rare cases, refractory hypercalcemia requires emergent surgery. Long standing hypercalcemia can risk damage to many end organs, especially the kidneys. Metastatic malignancy should be considered in severe and/or refractory cases.

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The Natural History of Untreated Hyperparathyroidism

10

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Contents

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Introduction

Prior to the introduction of serum multi-analysis in the 1970s, primary hyperparathyroidism (PHPT) was diagnosed by symptoms such as kidney stones, bone disease, and abdominal complaints. However, with the advent of blood chemistry panels, hypercalcemia is increasingly being detected in the "asymptomatic" stage. Today, the most common presentation of primary hyperparathyroidism in patients is the discovery of hypercalcemia during serum multi-analysis, which may be further investigated and determined to be caused by increased PTH levels [1]. The most common cause of hypercalcemia is PHPT caused by a parathyroid adenoma or hyperplasia functioning outside the bounds of normal physiological control mechanisms [2]. A solitary parathyroid adenoma is the cause of PHPT in over 80% of cases. In 15% of cases, hyperparathyroidism is secondary to multi-gland hyperplasia [3]. Besides calcium regulation, primary hyperparathyroidism also affects serum phosphate and bone health. Long-term hypercalcemia secondary to PHPT can cause renal, cardiovascular, and neuropsychiatric disease.

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Asymptomatic PTH and Whether or Not It Is Truly Asymptomatic

"Asymptomatic" hyperparathyroidism is now the most common presentation of PHPT. Normocalcemic primary hyperparathyroidism is increasingly being discovered, which is a normal calcium level in the face of an inappropriately elevated PTH levels [4]. Recent studies suggest that asymptomatic hyperparathyroidism may not in fact be so asymptomatic. The symptoms of PHPT are insidious in onset and frequently not appreciated by patients to be an acute disorder. Nephrolithiasis, osteoporosis, low energy level, fatigue, weakness, anorexia, sleep disorders, psychiatric symptoms ranging from depression and anxiety to psychosis, reduced social interaction, and diminished ability to complete daily activities have all been reported to be reversed following parathyroidectomy for "asymptomatic" hyperparathyroidism [4–6].

Effect of Hyperparathyroidism: Bone Disease

Chronically elevated PTH directly affects the skeletal system. Osteitis fibrosa cystica (OFC), the classical skeletal manifestations of PHPT, is relatively rare in Western countries and tends to occur only in patients with severe disease (Fig. 10.1).

In less developed countries, hyperparathyroidism more often presents as a severe, symptomatic disease [7]. OFC is characterized by overstimulation and proliferation of osteoclasts secondary to prolonged elevation of parathyroid hormone levels, which leads to increased bone resorption and thinning of the cortex. Hemorrhage into these cystic areas of resorption leads to hemosiderin deposition, giving the characteristic brown tumor appearance. Parathyroidectomy is associated with resolution and progressive reversal of this bony disease [8] (Fig. 10.2).

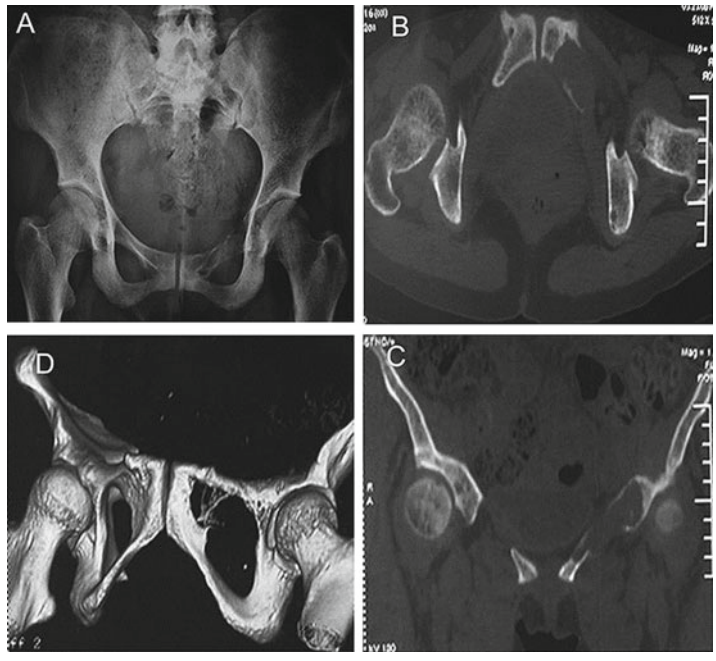

Fig. 10.1 Osteitis fibrosa cystica in the pelvis [8]

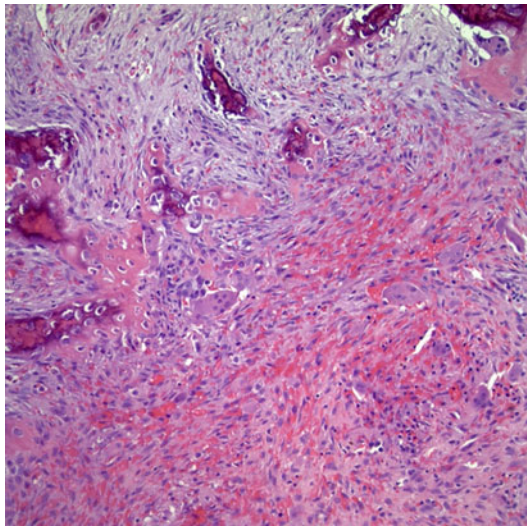

Fig. 10.2 Brown tumor of the bone in a patient with hyperparathyroidism [29]

A more common manifestation of hyperparathyroidism in Western countries is decreased BMD measured on DEXA scanning. PTH has a higher catabolic effect on cortical bone (distal radius and femur) compared to cancellous bone (lumbar spine). A 15-year prospective study of hyperparathyroidism treated with and without surgery demonstrated statistically significant increases in BMD loss of non-operated patients in the femoral head and the distal third of the radius, which are both primarily sites of cortical bone. In contrast, the lumbar spinal BMD, composed primarily of cancellous bone, was relatively preserved. In patients treated with parathyroidectomy, BMD increased from baseline values after 15-year follow-up [9].

Studies investigating skeletal microarchitecture in the setting of PHPT have demonstrated a loss of cortical bone with preservation of the trabecular architecture of cancellous bone. In PHPT, there is a marked increase in cortical porosity, which may lead to increased bone fragility, especially in cortical bone [10].

Vitamin D deficiency is increasingly recognized as a widely prevalent condition. Recent research suggests that the prevalence vitamin D deficiency in the USA and other Western countries is over 40% [11]. In the setting of vitamin D deficiency, the anabolic effect of elevated PTH on trabecular bone (increased number, volume, and interconnectivity of trabeculae) and its catabolic effect on cortical bone (cortical width thinning) are exacerbated [12]. Three-dimensional analysis of cancellous bone specimens suggests that PHPT helps stabilize and reduce trabecular thinning in postmenopausal women [13] (Fig. 10.3).

The anabolic effect of elevated PTH on trabecular bone formation does not reduce the incidence of fractures in bones with predominantly trabecular architecture (e.g., vertebral column). In a retrospective study of PHPT patients ($N=407$) over a 28-year period, mild PHPT resulted in a statistically significant increased risk of vertebral fractures. In addition, this study showed that there was an increased risk of distal radius, rib, pelvic, and any-site fractures. The study did not demonstrate a statistically significant increase in hip fractures [14] (Fig. 10.4).

Effects of Hyperparathyroidism: Renal Disease

In the kidney, PTH regulates serum calcium and phosphate at the proximal and distal convoluted tubules of the nephron. The vast majority of phosphate is reabsorbed in the proximal convoluted tubules; in the proximal tubules, PTH works to internalize the Na-PO4 transporter, thereby increasing phosphate excretion into the urine. In the distal convoluted tubules, PTH stimulates active reabsorption of calcium preventing excess calcium loss into the urine. In the setting of PHPT, prolonged hypercalciuria is a known risk factor for nephrolithiasis [15]. Between 20 and 50% of patients with hyperparathyroidism develop nephrolithiasis. The most common stone types in PHPT are calcium oxalate and calcium phosphate. PHPT can also cause nephrocalcinosis, which is a deposition of calcium-phosphate complexes in the parenchyma of the kidney itself. Current recommendations from the Fourth International Workshop on PHPT recommend imaging of the kidney of patients with asymptomatic PHPT for subclinical stone disease and

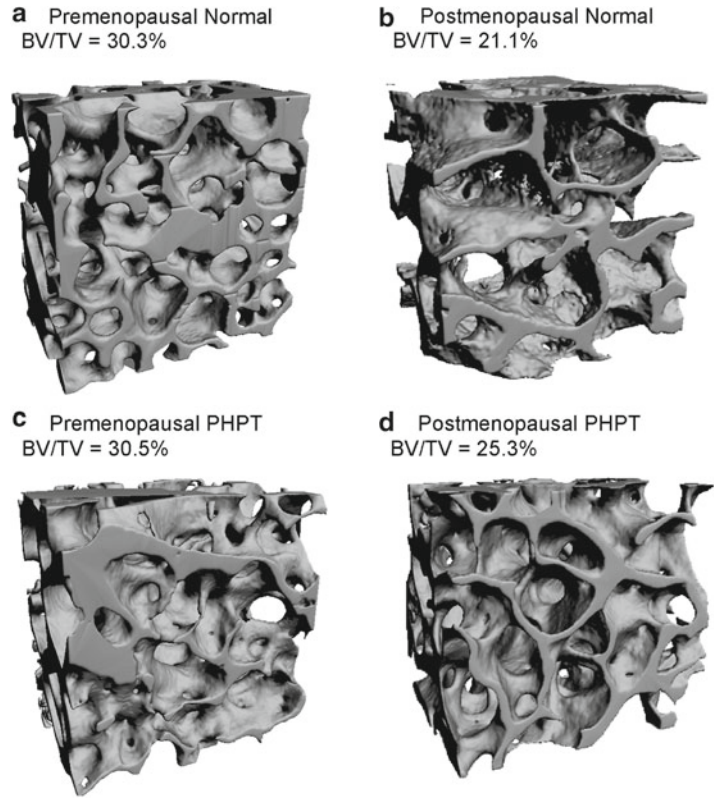

Fig. 10.3 Cancellous bone architecture in (**a**) normal premenopausal women, (**b**) normal postmenopausal women, (**c**) premenopausal PHPT women, and (**d**) postmenopausal PHPT women [13]

nephrocalcinosis, with positive imaging constituting an indication for parathyroidectomy [4].

Hyperparathyroidism can cause metabolic derangements, such as type 2 metabolic acidosis. PTH decreases bicarbonate reabsorption in the proximal tubule. Chronic PTH elevation reduces serum bicarbonate levels and causes reactive hyperchloremia [16]. This is why chloride elevation can be a subtle marker of PHPT in cases where the classic calcium/PTH relationships are absent. The severity of metabolic acidosis can be the most severe approximately 48 h after parathyroidectomy [17].

Effects of Hyperparathyroidism: Cardiovascular Disease

In a Scandinavian study, patients with moderately severe to severe PHPT demonstrated a higher mortality when compared to patients with normal serum PTH and calcium. The elevation in mortality rate diminished over time following parathyroidectomy. The mortality of patients with mild PHPT was not statistically different compared to the age- and sex-matched control population without PHPT [18]. Vestergaard et al. evaluated a group of Danish residents (N=674) diagnosed with PHPT as defined by elevated serum calcium and serum PTH in the upper one-third of the normal range or elevated beyond the normal range. In the decade preceding parathyroidectomy, PHPT patients had a significantly higher rate of myocardial infarction (MI) compared to matched controls (relative risk 2.5). MI incidence returned to control levels approximately 1 year after the patient underwent parathyroidectomy [19]. Hypertension has frequently been associated with PHPT; yet studies have not shown clear evidence of hypertension reversal following parathyroidectomy. Other studies have shown serum calcium and PTH levels to be independent predictors of coronary heart disease.

Left ventricular hypertrophy (LVH), one of the strongest predictors of cardiovascular morbidity and mortality, is a frequent finding in

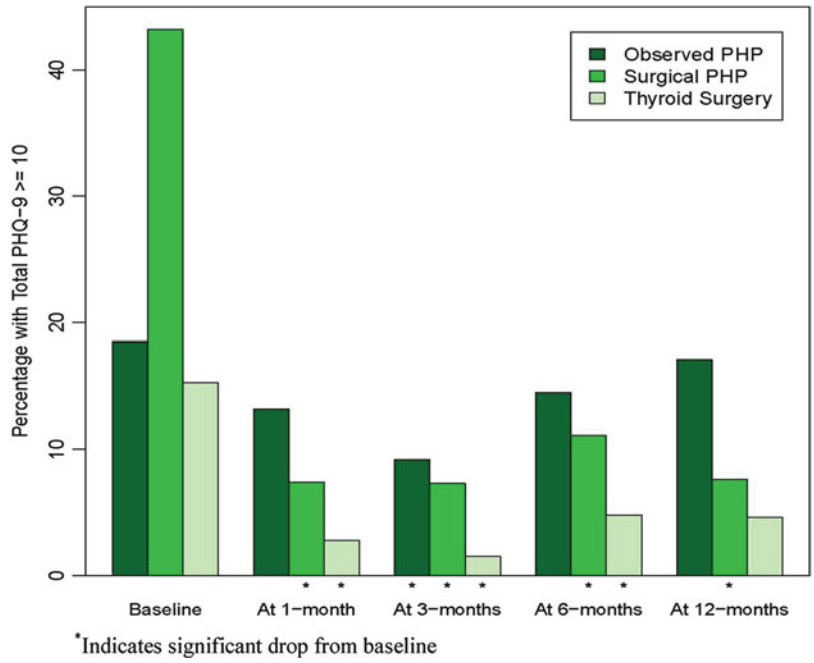

Fig. 10.4 PHQ-9 scores >10 (used to assess depression) at baseline, 1 month, 3 months, 6 months, and 1 year for both surgical (parathyroid and thyroid surgery) and observational groups [21]. *"asterisk"* indicates significant drop from baseline

PHPT. Piovesan et al. showed that PHPT is associated with increased left ventricular mass index (LVMI) over age-, sex, and blood pressure-matched controls; moreover, a linear relationship could be observed between LVMI and serum PTH. PTH was the strongest independent predictor of LVMI relative to calcium, phosphate, systolic blood pressure, and diastolic blood pressure. In the same study, reduction of left ventricular hypertrophy usually followed parathyroidectomy and normalization of serum PTH levels [20].

Hyperparathyroidism has been associated with structural and functional changes in carotid vasculature. In one study, patients with PHPT had increased carotid intima-medial thickness (IMT) when compared to controls. IMT is considered a subclinical predictor of systemic atherosclerotic vascular disease, and increased IMT has been associated with coronary and cerebrovascular events [21]. In another study, reduced carotid distensibility was also associated with elevated PTH levels [22]. A 2009 study assessing the effect of hyperparathyroidism on carotid vasculature demonstrated structural and functional changes in carotid vasculature. This study showed that patients with PHPT have increased IMT over controls. Interestingly, neither calcium nor PTH was associated with IMT in this study, which raises questions regarding the mechanism of increased IMT. Reduced carotid distensibility was also seen with elevated levels of PTH, and the degree of PTH elevation was shown to be an independent predictor of carotid stiffness [22].

Effects of Hyperparathyroidism: Neuropsychiatric Disease

It has long been understood that classical PHPT causes neuropsychiatric disease. Major depressive disorder is seen in almost one-third of patients with PHPT [23]. In one case–control study that measured major depression disorder symptoms using a questionnaire, parathyroidectomy was associated with a significant reduction of depressive symptoms either when compared to

patients with PHPT who were merely observed (nonsurgical treatment) or when compared to patients undergoing thyroid surgery. The reduction in major depression symptoms was sustained throughout the first year of follow-up. Of note, this study also reported that disease severity, as indicated by serum calcium levels, was related to the likelihood of depression [23].

PHPT has also been associated with diminished quality of life (QOL). In a prospective study over a 10-year period, patients with PHPT experienced a reduction in neuropsychiatric symptoms (e.g., fatigue, depression, forgetfulness, irritability, mood swings) after parathyroidectomy compared to controls. This may suggest that neuropsychiatric symptoms and reduced QOL are disease-specific symptoms that improve upon biochemical cure of patients [24].

Finally, PHPT has also been shown in various studies to affect cognitive function. A prospective study of postmenopausal women with PHPT demonstrated that visual memory, concentration, auditory attention, and mental manipulation were not impaired in patients with PHPT. However, when compared to the postmenopausal control group, postmenopausal women with PHPT performed worse on verbal memory and nonverbal abstraction evaluations. Interestingly following parathyroidectomy, nonverbal abstractions and some aspects of verbal memory improved to control levels [25].

Summary

Untreated primary hyperparathyroidism leaves patients at risk for many conditions, which are preventable with parathyroid surgery. If not treated, primary hyperparathyroidism patients experience poor quality of life and may suffer from cardiac, musculoskeletal, genitourinary, and psychosomatic issues.

Guidelines

Fourth International Workshop Guidelines for Diagnosis of Asymptomatic Primary Hyperparathyroidism [26]:

- Reference ranges ought to be established for serum PTH in individuals with normal levels of vitamin D.
- Second- and third-generation PTH assays are helpful in the diagnosis of PHPT
- Normocalcemic PHPT is a variant of the more common presentation of PHPT with hypercalcemia.
- Serum concentration of 25-vitamin D should be measured, and vitamin D deficiency, if detected, should be treated as part of the patient's overall management.
- Genetic testing has potential utility in the differential diagnosis of familial hyperparathyroidism or hypercalcemia.

Best Practices [27, 28]

- Recommend for a more extensive evaluation of the skeletal and renal systems.
- Allow skeletal and/or renal involvement to become part of the guidelines for surgery.
- Monitor those who do not meet guidelines for parathyroid surgery.
- All patients with PHPT who meet surgical criteria should be referred to an endocrine surgeon to discuss treatment.
- Patients who do not meet surgical criteria and for whom there are no medical contraindications to surgery may request consultation by an endocrine surgeon.
- Imaging is a nondiagnostic procedure; it is utilized to help localize the lesion and optimize surgical planning.
- The incidence of hereditary forms of PHPT may be underrecognized and needs to be assessed with increased vigilance.

- Surgery is likely to benefit patients due to high cure rates, low complication rates, and the likelihood of reversing skeletal manifestations.

Expert Opinion

It is unethical to leave primary hyperparathyroidism patients untreated. No treatment increases their risk of morbidity and/or mortality from fracture, heart attack, stroke, or psychiatric causes. It is incumbent upon frontline providers to recognize hypercalcemia when incidentally discovered and commence an appropriate evaluation and referral for treatment. Hypercalcemia should not be ignored, and it should be considered in patients that present with vague, nonspecific somatic complaints.

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Hypoparathyroidism

11

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Contents

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Introduction

Hypoparathyroidism is a rare disorder characterized by low serum calcium, increased serum phosphorus, and low or inappropriately low-normal serum parathyroid hormone. The estimated prevalence of this condition in the U.S. is 37 per 100,000 person-years [1], with a projected affected population of about 77,000 individuals [2]. The estimated prevalence of postsurgical hypoparathyroidism in Denmark is 22 per 100,000 person-years, and the prevalence of nonsurgical hypoparathyroidism 2.3 per 100,000 person-years [3, 4]. The estimated incidence of hypoparathyroidism in Denmark is 0.8 per 100,000 person-years [5]. Estimates of prevalence and incidence of hypoparathyroidism in other countries are currently not available.

This condition is most often acquired, but may be inherited. The acquired form occurs due to the inadvertent removal of, or damage to, the parathyroid glands or their blood supply at the time of neck surgery for thyroid disease, head and neck cancer, or parathyroid disease in about 75 % of cases. Of the remaining cases, the most common cause in adults is thought to be autoimmune disease, either in an isolated form affecting only the parathyroid glands, or in a polyglandular form affecting multiple other endocrine organs. Rare infiltrative disorders due to metastatic disease or iron or copper overload, ionizing radiation

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exposure, and rare genetic disorders explain the remaining cases.

This chapter describes the recognized causes, symptoms, complications, and treatment of hypoparathyroidism. It discusses the differential diagnosis of hypoparathyroidism, and then reviews the classical symptoms of hypoparathyroidism, which are attributed largely to hypocalcemia. Newer information on complications and comorbidities will then be described, followed by detailed discussion of the treatment of hypoparathyroidism.

Causes of Hypoparathyroidism

Hypoparathyroidism is due to a wide variety of causes (Table 11.1). By far the most common cause of hypoparathyroidism in adults is postsurgical hypoparathyroidism [6]. Postsurgical hypoparathyroidism occurs after neck surgery, but not only surgery targeting the parathyroid glands. The parathyroid glands may be adversely affected by compromised blood supply after manipulation during surgery of other neck

Table 11.1 Classification of Hypoparathyroidism

Category of pathology	Genetic defect
Parathyroid gland destruction	
Surgery	
Radiation therapy	
Infiltration	
Autoimmune: isolated or APECED	*AIRE*, 21q22.3
Reduced parathyroid gland function	
Autosomal dominant hypocalcemic hypercalciuria	*CASR*, 3q13.3-21
PTH gene mutation	*PTH*, 11p15
Autoantibodies to *CASR*	
Disorders of parathyroid gland formation	
DiGeorge sequence	*TBX1*, 22q11; 10p; intrauterine exposure to alcohol, diabetes, isotretinoin
Hypoparathyroidism with sensorineural deafness and renal dysplasia (HDR)	*GATA3*
Hypoparathyroidism-retardation-dysmorphism (HRD), Kenny-Caffey/Sanjad-Sakati syndromes	*TBCE*
Autosomal recessive/dominant hypoparathyroidism	*GCM2*
X-linked hypoparathyroidism	Xq27
Other causes of hypoparathyroidism	
Mitochondrial disease	Mitochondrial tRNA
Burns	
Resistance to parathyroid hormone	
Pseudohypoparathyroidism	*GNAS*
Transient pseudohypoparathyroidism of the newborn	
Hypomagnesemia	

APECED autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, *AIRE* autoimmune regulator gene, *CASR* calcium sensing receptor gene, *PTH*, parathyroid hormone gene, *TBX1* T-BoX protein 1 gene, *GATA3* GATA binding protein 3 gene, *TBCE* tubulin binding (folding) cofactor E gene, *GCM2* glial cells missing 2 gene, *tRNA* transfer RNA, *GNAS* Gs-alpha gene

structures, or by their inadvertent removal. Postsurgical hypoparathyroidism usually results in hypocalcemia within 24–48 h after surgery, and is usually temporary. Different centers report different rates of symptomatic hypoparathyroidism after thyroid cancer surgery, ranging from 25 to 80 % [7], whereas long-term postsurgical hypoparathyroidism is usually limited to less than 1–5 % of cases, depending on surgical expertise. The rate of post-thyroidectomy hypoparathyroidism increases with the stage of thyroid cancer, and is dependent on the extent of surgery, with about half of stage IV thyroid cancer patients suffering from postsurgical hypoparathyroidism.

Most patients with postsurgical hypoparathyroidism have the transient form of this disorder. Experience of the surgeon performing surgery is predictive of the incidence of postsurgical hypoparathyroidism. Immediate postoperative serum calcium and PTH levels may be useful in predicting which patients will develop permanent hypocalcemia due to postsurgical hypoparathyroidism [8].

Nonsurgical hypoparathyroidism may be due deficiency or excess of serum magnesium [9, 10]. Hypomagnesemia usually causes hypoparathyroidism when serum magnesium is less than 1.0 mg/dL. Up to 11 % of hospitalized patients may have hypomagnesemia, while up to 9 % may have hypermagnesemia [11]. Hypomagnesemia may be due to gastrointestinal losses associated with vomiting related to excessive alcohol intake, chronic diarrhea, steatorrhea, malabsorption, or intestinal resection, or renal tubular losses due to medications such as furosemide, aminoglycosides, cisplatin, cyclosporin, amphotericin B, pentamidine, tacrolimus, or proton pump inhibitors [12]. Rare genetic disorders such as Gitelman syndrome may contribute to hypomagnesemia. Hypomagnesemia occurs frequently in critically ill patients, which contributes to the hypocalcemia frequently seen in intensive care unit patients. Hypermagnesemia may occur in late-stage chronic kidney disease in patients treated with magnesium antacids, enemas, or infusions, or acute renal failure associated with rhabdomyolysis or tumor lysis syndrome [13].

Primary intestinal hypomagnesemia results from a rare inherited disorder causing magnesium malabsorption leading to hypomagnesemia in early infancy. This condition is thought to primarily occur due to deficient intestinal magnesium absorption, but there may also be defects in renal magnesium reabsorption. Patients usually present with neurological symptoms, including tetany, muscle spasms, and seizures due to both hypomagnesemia and hypocalcemia associated with hypoparathyroidism. Lifelong high oral intake of magnesium supplements decreases symptoms and restores serum calcium levels to normal. Mutations in the TRMP6 gene on chromosome 9 have been identified to cause this disorder [14, 15]. The TRMP6 protein is a member of the transient receptor membrane potential channel family that complexes to TRPM7, a calcium- and magnesium-permeable cation channel.

Other acquired causes of hypoparathyroidism are much rarer. Hypoparathyroidism may result from metastases to the parathyroid glands in extremely rare circumstances [16]. Infiltration and destruction of the parathyroid glands by iron overload may occur in hemochromatosis, or thalassemia requiring multiple blood transfusions [17]. Copper overload occurring due to Wilson's disease may also result in hypoparathyroidism [18].

External beam radiation therapy to the neck for treatment of malignant disease, or radioactive iodine therapy for Graves' disease, may also rarely result in destruction of the parathyroid glands [19].

Inherited causes of hypoparathyroidism include autosomal dominant hypocalcemia with hypercalciuria (ADHH), a condition in which there is a gain-of-function mutation in the CaSR gene [20]. This type of mutation changes the threshold of PTH secretion by parathyroid cells in response to circulating ionized calcium, leading to low or inappropriately low-normal PTH secretion despite hypocalcemia. Most of the mutations reported to date affect the extracellular N-terminal or transmembrane domains of the receptor. The mutant receptors may show both increased receptor sensitivity to calcium and increased maximal signal transduction capacity.

Since this activating mutation is also expressed in the CaSR protein on proximal renal tubular cells in the thick ascending limb of Henle, absolute or relatively increased 24-h urinary calcium excretion is a hallmark of the disorder. Most patients with ADHH are asymptomatic and have mild hypocalcemia with significant hypercalciuria, but occasional patients may present with moderate or severe hypocalcemia. This form of CaSR-mediated hypoparathyroidism may cause increased risk of nephrocalcinosis compared to other forms of hypoparathyroidism. In one series, almost half of the patients evaluated had nephrocalcinosis associated with hypercalciuria [21]. Calcium and calcitriol supplementation must therefore be carefully monitored in this condition.

Occasional reports have described patients with CaSR gene gain-of-function mutations associated with a Bartter-like syndrome, suggesting that the CaSR protein may also play a role in sodium chloride regulation [22]. These patients present with hypocalcemia, hypercalciuria, and nephrocalcinosis, associated with hypokalemic alkalosis, renal salt wasting that may cause hypotension, hyperreninemic hyperaldosteronism, and increased urinary prostaglandin excretion. Extensive burns may also lead to upregulation of the CaSR, with lower than normal serum calcium suppressing PTH secretion, resulting in hypocalcemia and hypoparathyroidism.

Autoimmune hypoparathyroidism is thought to be the second most common form of adult acquired hypoparathyroidism. Isolated autoimmune destruction of the parathyroid glands may occur, resulting in idiopathic hypoparathyroidism, or autoimmune destruction may occur in association with other autoimmune conditions as part of autosomal recessive autoimmune polyglandular endocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED) [23]. This syndrome is caused by mutations in the autoimmune regulator AIRE gene, which results in abnormal thymic expression of tissue antigens, generation of autoreactive T-cells, ultimate loss of central tolerance to specific self-antigens, and the development of multiple autoimmune disorders [24]. Antibodies against the CaSR have been identified in some individuals with both idiopathic hypoparathyroidism and APECED syndrome [25, 26], but it is not yet clear if these antibodies are causative or simply markers of disease [27]. Idiopathic autoimmune hypoparathyroidism most often occurs in the teenage years or young adulthood, but may occur at any age. APECED usually presents in childhood, and is characterized by chronic mucocutaneous candidiasis in addition to variable expression of endocrine and other autoimmune diseases. Variation in the clinical phenotype of individuals with identical mutations in *AIRE* is incompletely understood, but this suggests that other genetic loci or environmental factors are important in development of the phenotype.

Hypoparathyroidism may be diagnosed at birth or during childhood due to a variety of genetic mutations causing congenital syndromes, the most widely known being the DiGeorge (velocardiofacial) sequence [28]. This disorder is caused by abnormal development of neural crest cells in the third and fourth branchial pouches. In 90 % of cases, the syndrome is caused by heterozygous chromosomal deletion of the TBX1 gene in the region of chromosome 22q11. Thirty-five genes have been identified in this region, so deletion of other genes, alone or in combination, could also cause this syndrome, but the TBX1 gene is a major determinant of cardiac, thymus, and parathyroid cell phenotypes. A region on chromosome 10p (DiGeorge critical region II) has also been linked to the sequence. DiGeorge syndrome is associated with distinctive facial abnormalities, cleft lip and/or palate, conotruncal cardiac anomalies, and mild to moderate immune deficiency. Hypocalcemia due to hypoparathyroidism has been reported in 17–60 % of affected children [29]. DiGeorge syndrome is estimated to occur in as many as 1:2000–1:3000 births, with the incidence rate of new mutations estimated at 1:4000–1:6000. Because the clinical phenotype varies, findings may be subtle and therefore overlooked, and mild hypocalcemia may be easily missed. In one study of adults with chromosome 22q11.2 deletion, about half were hypocalcemic, with a median age of presentation of 25 years, and a maximum age of diagnosis of up to 48

years [30]. This disorder may rarely be diagnosed for the first time as late as the mid-60s, with late onset of mild hypocalcemia, and is not infrequently diagnosed in affected parents in their 20s or 30s after the birth of an affected child.

Finally, a variety of other rare genetic or inherited disorders may cause hypocalcemia that is usually recognized in infancy or childhood. Familial isolated hypoparathyroidism due to autosomal recessive or dominant mutations in the pre-proPTH gene on chromosome 11p15 [31, 32], or parathyroid gland dysgenesis due to mutations in various transcription factors regulating parathyroid gland development such as GCMB (glial cells missing B) [33] or GCM2 (glial cells missing 2) [34], GATA3 [35, 36], or Sry-box 3 (SOX3) [37], are thought to be very rare. Autosomal dominant hypoparathyroidism associated with deafness and renal anomalies has been linked to mutations in the GATA3 gene on chromosome 10p14-10-pter [35, 36]. Hypoparathyroidism has been very rarely associated with X-linked recessive mutations on Xq26-27, leading to disruption of SOX3 transcription [37]. The syndrome of autosomal recessive hypoparathyroidism, growth and mental retardation, and dysmorphism due to mutations in the TBCE gene on chromosome 1q42-q43 is another very rare cause of hypoparathyroidism [38]. Hypoparathyroidism with metabolic disturbances and congenital anomalies has been associated with rare maternal mitochondrial gene defects [39, 40].

Symptoms of Hypoparathyroidism

Regardless of the cause of their hypoparathyroidism, patients most often present with tingling paresthesias about their finger and toe tips, lips, or tongue, and diffuse muscle cramps [41, 42]. Occasionally patients develop more severe cramps or carpopedal spasm (tetany). More severely affected patients may develop seizures, bronchospasm, laryngospasm, or cardiac rhythm disturbances due to prolongation of their QT interval related to hypocalcemia. Occasional patients with mild hypoparathyroidism may be asymptomatic much or most of the time. Rare severely affected patients may die due to untreated hypocalcemia. The severity of symptoms reported generally correlates with the severity of hypocalcemia. Table 11.2 describes recognized symptoms and signs of hypocalcemia that may be seen in patients with hypoparathyroidism.

Table 11.2 Symptoms and signs of hypocalcemia associated with hypoparathyroidism

Symptoms
Circumoral and finger and toe tip tingling paresthesias
Increased neuromuscular irritability
Tetany
Muscle cramps and twitching
Muscle weakness
Abdominal cramps
Laryngospasm
Bronchospasm
Altered CNS function
Altered mental functioning
Seizures of all types
Papilledema or pseudotumor cerebri
Choreoathetoid movements
Depression
Coma
Congestive heart failure
Generalized fatigue
Signs
Chvostek's sign
Trousseau's sign
Prolongation of QTc interval
Cataracts
Basal ganglia and other intracerebral calcifications

Complications of Hypoparathyroidism

Complications of hypoparathyroidism are thought to depend in part on treatment for the disorder, because most patients are unable to function well or survive without treatment for very long. Most patients require treatment with high-dose calcium and vitamin D supplementation to correct their hypocalcemia. Recent studies have shown that a variety of comorbidities is associated with hypoparathyroidism. Commonly recognized

complications include hypocalcemia, hypercalcemia, hypercalciuria, calcium-containing kidney stones, cataracts, and basal ganglia and other intracerebral calcifications [41].

Recent long-term studies using the Danish National Patient Registry of patients with hypoparathyroidism [3, 5] have shown a threefold increased risk of renal disease, with a threefold increased risk of renal insufficiency in postsurgical cases, and sixfold increase in nonsurgical cases. Patients in the registry had a fourfold increased risk of hospitalization for calcium-containing kidney stones. Cardiovascular risk in patients with postsurgical hypoparathyroidism was not increased compared to the general population, but was increased twofold in the nonsurgical cases, with borderline increased risk of stroke and cardiac dysrhythmia.

In another study using the same national registry [4], neuropsychiatric disease was increased 2.45-fold in both postsurgical and nonsurgical patients, with depression and bipolar disorder increased twofold in postsurgical cases. Risk of infections was increased 1.42-fold in postsurgical patients, and 1.94-fold in nonsurgical cases. The most common infection seen was urinary tract infection (UTI), with a borderline increase in UTI in postsurgical patients, and a 3.84-fold increased risk in nonsurgical patients. Risk of hospitalization for seizures was increased by 3.82-fold in postsurgical patients, and tenfold in nonsurgical cases. Risk of cataracts was seen only in nonsurgical cases, with a 4.2-fold increased risk. Fractures overall did not differ between patients with postsurgical or nonsurgical hypoparathyroidism and the general population, but there was a mildly increased risk of upper extremity fractures in nonsurgical patients, and a decreased risk of upper extremity fractures in postsurgical patients.

Treatment of Hypoparathyroidism

Guidelines for the clinical management of hypoparathyroidism have recently been published [40, 41]. Treatment of hypoparathyroidism is intended primarily to improve or eliminate symptoms, reverse increased skeletal mineralization to the degree it is present, heal osteomalacia if present, maintain minimum goal-range serum total and ionized calcium, reduce hyperphosphatemia, minimize hypercalciuria to 24-h urine calcium of <300 mg, and avoid renal dysfunction, kidney stones, nephrocalcinosis, cataracts, and basal ganglia and other intracerebral calcifications [42, 43].

Acute Hypoparathyroidism

Patients who require emergent or urgent treatment due to symptoms such as severe muscle cramps, tetany, seizures, laryngospasm, bronchospasm, cardiac rhythm disturbances, altered mental status, or severe hypocalcemia, require intravenous calcium, usually given as calcium gluconate. One standard approach is to add ten 10-mL ampules of calcium gluconate, with 93 mg elemental calcium per ampule, to 900 mL of 5 % dextrose, and to slowly infuse 10 mL over 10 min to improve symptoms, with repeat infusions given once or twice more as needed [42, 43]. Calcium chloride is usually not recommended for intravenous replacement due to the risk of venous and soft tissue irritation associated with extravasation, unless a central venous line is present [44]. Cardiac monitoring is recommended during intravenous calcium infusion [45].

Because hypocalcemia will usually recur rapidly after 2–3 bolus infusions if no further treatment is given, a maintenance infusion of calcium gluconate at the same concentration is then started at 10–100 mL/h to minimize symptoms and improve serum calcium to the lower end of the normal range at around 8.5 mg/dL (2.12 mmol/L), with an ionized calcium of around 4 mg/dL (1.0 mmol/L) [45, 46]. The infusion rate is usually titrated to give 0.3–1.0 mg elemental calcium/kg/h.

Once the patient is stabilized with an intravenous calcium infusion, oral calcium supplementation is then started, giving the patient at least 500 mg elemental calcium three to four times a day. The calcium gluconate infusion is gradually tapered as serum calcium approaches the target level at the lower end of the normal range, the

patient's symptoms improve, and oral calcium supplements are continued.

If the serum 25-hydroxyvitamin D level is greater than 20 ng/mL, vitamin D3 supplementation is frequently started at 1000 International Units each day to improve absorption of the calcium supplements. If serum 25-hydoxyvitamin D is less than 20 ng/mL, higher-dose vitamin D3 supplementation is typically started, often at 50,000 International Units once weekly for 2 months to restore vitamin D levels to the desired range of 30–100 ng/mL [47].

Chronic Hypoparathyroidism

If hypoparathyroidism does not resolve after the acute episode, management of chronic hypocalcemia is required. Usually this involves long-term high-dose oral calcium and vitamin D supplementation, sometimes for life, with thiazide-type diuretics or magnesium supplementation as needed. Recent guidelines for management of hypoparathyroidism recommend reasonable goals for management include maintenance of (1) serum calcium in the low-normal range, (2) serum phosphorus in the high-normal range, (3) 24-h urine calcium less than 300 mg, and (4) serum calcium x phosphate product less than 55 mg^2/dL^2 [42, 43].

If serum magnesium level is decreased, the total body magnesium deficit is usually very large, but poorly reflected by the serum magnesium level, because magnesium is mostly an intracellular cation. Supplementation with magnesium usually takes months to fully replete body stores. As serum magnesium is gradually replaced, serum calcium and parathyroid levels will return toward normal.

Once serum calcium, phosphorus, vitamin D, and magnesium are stabilized, patients need to be monitored periodically. Table 11.3 summarizes the recommended frequency of follow-up of various biochemical and imaging studies for patients being followed for chronic hypoparathyroidism.

Table 11.3 Frequency of monitoring of biochemical and imaging tests in hypoparathyroidism during treatment

Serum Ca, P, and Cr	During initial treatment phase: weekly to monthly
	After treatment stabilization: twice yearly to yearly
Follow-up evaluations	During initial treatment phase: every 1–2 weeks
	After treatment stabilization: every 3–6 months
24-h urine Ca/Cr	Twice yearly
Kidney imaging	Yearly until stable, then as indicated
Ophthalmology evaluation	Yearly
Brain imaging	As indicated

Calcium

Oral calcium supplements of any type will restore serum calcium toward normal. In general, calcium carbonate or calcium citrate is used most commonly because they are widely available and relatively inexpensive [48, 49]. Calcium carbonate contains 40% elemental calcium by weight, and calcium citrate 21% calcium by weight. Calcium citrate absorbs well when stomach acid is reduced for any reason, including proton pump inhibitor therapy for gastroesophageal reflux, so is often preferred in patients with hypoparathyroidism [50].

Calcium supplements are given in divided doses each day, typically two and four times a day, with dosing often given at mealtimes to enhance absorption. Starting doses are usually 500–1000 mg elemental calcium two or three times each day, and titrated upward as needed based on tolerability, compliance, and the clinical target range. Many patients with hypoparathyroidism require 3000–5000 mg elemental calcium each day, but some need as little as 1000 mg, and some need as much as 9000 mg [44]. Rare patients may need frequent intravenous calcium and/or magnesium infusions several times a week to prevent significant hypocalcemia.

Vitamin D

Commonly, calcium supplementation alone is insufficient to achieve serum calcium in the range of 8.0–8.5 mg/dL (2.0–2.13 mmol/L). In this

case, vitamin D supplementation is usually started. If renal function is normal, vitamin D2 (ergocalciferol) or D3 (cholecalciferol) is usually started at 1000–4000 International Units once each day, or alternatively, 50,000 International Units once each week to several times each week as needed, depending on intestinal absorption efficiency [47]. The serum 25-hydroxyvitamin D target level is usually 30–100 ng/mL, but may be lower than this in some patients. Patients with severe hypoparathyroidism typically require higher doses of vitamin D. Care must be used with vitamin D2 or D3, however, as their half-life is prolonged at 2–3 weeks due to storage in body fat, and toxic serum levels of 25-hydroxyvitamin D causing hypercalcemia may take up to 6–9 months to clear after supplementation is stopped. Commercial parenteral vitamin D is no longer available in the U.S., but some academic hospital pharmacies produce high-concentration intravenous vitamin D3 based on clinical need.

Because of concerns regarding vitamin D toxicity, active vitamin D in the form of calcitriol (1,25-dihydroxyvitamin D) 0.25 mcg once or twice a day is often started in place of vitamin D2 or D3 in the U.S., whereas alfacalcidol (1α-hydroxyvitamin D) in low doses is used in Europe and other countries [47]. The maximum dose of calcitriol used is usually about 2.0 mcg each day. The half-life of active forms of vitamin D is on the order of 1–3 days, so improvement in calcium absorption or offset of vitamin D action occurs rapidly. These doses will rapidly increase serum calcium within 2–3 days [51–55].

Because vitamin D stimulates absorption of both calcium and phosphorus, hyperphosphatemia may be worsened with vitamin D supplementation in any form. Patients with hypoparathyroidism often have baseline hyperphosphatemia due to the lack of PTH. In some cases, low-phosphorus diets or phosphate binders may be required to control hyperphosphatemia.

Thiazide Diuretics

Patients who develop hypercalciuria while on calcium and vitamin D maintenance supplementation, or who are unable to achieve or maintain serum calcium at or near their target range, may benefit from addition of a thiazide-type diuretic to reduce urinary calcium loss. Thiazide-type diuretics increase renal tubular calcium reabsorption and thereby reduce urinary calcium excretion [56–60]. Doses of hydrochlorothiazide or chlorthalidone of 12.5–25 mg each day are commonly used for this purpose, and may be beneficial, but some patients may require as much as 50 or 100 mg to decrease their 24-h urine calcium to less than 300 mg. Hypokalemia may result from long-term or higher-dose thiazide-type diuretic use, limiting the use of these medications. Some patients with low blood pressure at baseline are not able to tolerate them due to further volume contraction.

Parathyroid Hormone (PTH)

Parathyroid hormone therapy has the great advantage that it replaces the absent or deficient hormone in patients with hypoparathyroidism. This should reduce the need for high-dose calcium and vitamin D supplementation, and thereby minimize the risk of hypercalcemia, hyperphosphatemia, and hypercalciuria.

PTH 1-34

Once or twice daily injections of PTH 1-34 (teriparatide) have been used off-label in short term trials to normalize serum and urine calcium and phosphorus in adults and children with hypoparathyroidism. This therapy is not approved by the FDA for treatment of hypoparathyroidism.

A crossover pilot study [61] in ten adults demonstrated that PTH 1-34 given by single daily injection maintained serum and urinary calcium in the normal range over 24 h for 10 weeks, and resulted in lower urinary calcium than calcitriol for a given level of serum calcium. A subsequent study of PTH 1-34 given twice daily to adults for 14 weeks [62] was shown to treat hypoparathyroidism effectively, with reduced total daily calcium requirement, increased bone turnover, and reduced bone pain compared to once daily dosing. A subsequent long-term study [63] randomized 27 adults to twice daily PTH 1-34 vs. calcitriol for 3 years, and showed that serum calcium was able to be maintained in the low-normal to just-below normal range, without a difference

in serum or urine calcium levels between groups. PTH 1-34 increased markers of bone turnover by about twofold above normal, but DXA bone mineral density (BMD) did not change. The calcitriol-treated group did not show a change in markers of bone turnover, but did experience an increase in lumbar spine BMD.

The most recent adult study with PTH 1-34 [64] compared continuous infusion by insulin pump to twice daily injection in 8 adults with postsurgical hypoparathyroidism over 6 months in an open-label crossover study. This study showed that continuous infusion resulted in less fluctuation in serum calcium over time, >50 % reduction in urine calcium, and 65 % reduction in PTH 1-34 dose required to maintain normocalcemia compared to injection. Continuous infusion resulted in higher serum magnesium, normal urine magnesium, and reduced need for magnesium supplements. Pump delivery normalized serum markers of bone turnover, and lowered urinary markers of bone turnover, compared to twice daily injection.

Three studies in children have shown similar benefits as in adults. A 14-week study in 14 children [65] demonstrated better metabolic control with twice daily than once daily PTH 1-34, but with no difference in markers of bone turnover. A 3-year study in 12 children [66] showed that PTH 1-34 can effectively maintain serum calcium within the normal range or just below. Similar to the adult 3-year study, markers of bone turnover increased in the PTH 1-34 group compared to calcitriol, but in spite of this, the distal 1/3 radius DXA BMD decreased in the PTH 1-34 group. 24-h urine calcium excretion remained within the normal range in both groups. A 6-month crossover study in 12 children and young adults with congenital hypoparathyroidism aged 7–20 years [67] compared continuous PTH 1-34 infusion by insulin pump with twice daily injection. Continuous infusion resulted in near-normalization of mean serum and urine calcium, and reduced serum markers of bone turnover. Fluctuations in serum and urine calcium and magnesium were minimized with continuous infusion compared to twice daily injection. PTH 1-34 dose requirement was markedly reduced with pump delivery, and magnesium supplementation also reduced.

PTH 1-84

The pivotal 6-month phase III clinical trial with PTH 1-84 (Natpara) [68] led to FDA approval of this drug for treatment of hypoparathyroidism on January 23, 2015. This double-blind, placebo-controlled, randomized phase 3 study recruited patients with hypoparathyroidism of ≥18 months duration who were aged 18–85 years from 33 sites in eight countries. After an optimization period, during which calcium and active vitamin D doses were adjusted to achieve consistent albumin-corrected serum calcium levels, patients were randomized 2:1 to 50 μg per day of rhPTH(1-84) or placebo for 24 weeks. Active vitamin D and calcium were progressively reduced, while rhPTH(1-84) was titrated up from 50 to 75 μg and then to 100 μg during the first 5 weeks of the study. The primary endpoint was the proportion of patients at week 24 who achieved a 50 % or greater reduction from baseline in their daily dose of oral calcium and active vitamin D, while maintaining a serum calcium concentration greater than or the same as baseline concentrations and less than or equal to the upper limit of normal, after analysis by intention to treat. A total of 134 eligible patients were recruited and randomly assigned to rhPTH(1-84) ($n=90$) or placebo ($n=44$). Six patients in the rhPTH(1-84) group and seven in the placebo group dropped out before the end of the study. A total of 48 (53 %) patients in the rhPTH(1-84) group achieved the primary endpoint compared with one (2 %) patient in the placebo group. The proportions of patients who had at least one adverse event were similar between groups, with 84 (93 %) of patients in the rhPTH(1-84) group and 44 (100 %) of patients in the placebo group having hypocalcaemia, muscle spasm, paresthesias, headache, and nausea as the most common adverse events. The proportions of patients with serious adverse events were also similar between the rhPTH(1-84) group, with ten (11 %) patients, and the placebo group, with four (9 %) patients.

This study demonstrated that 50 μg, 75 μg, or 100 μg per day of rhPTH(1-84), administered subcutaneously in the outpatient setting, was efficacious and well tolerated as a PTH replacement therapy for patients with hypoparathyroidism.

PTH 1-84 has also been used in an open-label study at a fixed subcutaneous dose of 100 mcg every other day in 27 adults for 48 months [69]. PTH 1-84 treatment resulted in a 37 % reduction in calcium supplementation, and 45 % reduction in calcitriol requirements. Seven subjects were able to discontinue calcitriol completely. Serum calcium remained normal, and serum phosphorus and urinary calcium decreased. Lumbar spine BMD increased by 5.5 %, whereas total hip, femoral neck, and distal radius BMD remained stable. Serum markers of bone turnover increased threefold by 6–12 months, and then decreased to steady state levels by 30 months. Hypercalcemia occurred 11 times in 8 subjects over 4 years, with most episodes occurring in the first 6 months (1.9 % of all values), and resolving with appropriated adjustment of supplemental calcium and vitamin D.

PTH 1-84 therapy was used in a randomized study at a fixed subcutaneous dose of 100 mcg or placebo every day in 62 adults over 6 months as add-on therapy to conventional treatment [70, 71]. Compared to placebo, subjects treated with PTH 1-84 were able to reduce their calcium dose by 75 %, and active vitamin D dose by 73 %, without developing hypocalcemia. Hypercalcemia occurred frequently during down-titration of calcium and active vitamin D supplements after starting therapy. Plasma phosphate and urinary calcium and phosphate levels did not change over 6 months. Serum and urinary markers of bone turnover increased significantly as expected, and DXA BMD decreased mildly at the total hip, lumbar spine, and total body, but remained stable at the wrist.

Parathyroid Transplantation and Stem Cells

Parathyroid allograft transplants have been used in a few individuals who either previously or simultaneously underwent renal transplantation [72, 73]. Advances in stem cell technology may someday permit stem cells to be used to create new parathyroid tissue in patients where it is lacking.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion

Hypoparathyroidism is a rare disorder most often caused by anterior neck surgery. Awareness of the prevalence and comorbidities of this condition will help physicians and surgeons caring for patients with hypoparathyroidism to better understand the challenges faced by these patients. New therapies offer the potential to markedly improve care of patients with hypoparathyroidism.

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Part V

Parathyroid Diagnostic Imaging

12 Single-Photon Scintigraphic Imaging of the Parathyroid Glands: Planar, Tomography (SPECT), and SPECT-CT

Tracy L. Yarbrough, Twyla B. Bartel, and Brendan C. Stack Jr.

Contents

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Introduction

The ability to image the parathyroid glands with scintigraphy, and hyperplastic or adenomatous glands in particular, dates back to 1964 when Potchen and Sodee visualized a parathyroid adenoma using Se-75 selenomethionine in a 31-year-old male suffering from painful bone disease [55]. In the ensuing 45 years, imaging of the parathyroid glands evolved to include the administration of 99m-technetium sestamibi ("MIBI") followed by a planar scintigraphic technique. Today, the investigation of parathyroid function utilizing three-dimensional tomographic techniques has grown due to the increasing availability of cameras able to reconstruct volumetric data into axial, coronal, and sagittal planes. This technique, single-photon emission tomography

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(SPECT), has allowed for improved reader confidence in the detection of parathyroid disease largely due to the ability to differentiate overlying structures from abnormal parathyroid glands. Likewise, the increasing availability of hybrid cameras which incorporate both SPECT and computed tomography (CT) has engendered a rush to utilize this hybrid technique (SPECT-CT) for parathyroid localization as it allows for anatomic correlations and localizations that are translatable to a surgical approach. This chapter discusses the current literature regarding the use of planar, SPECT, and SPECT-CT in the evaluation of eutopic and ectopic parathyroid disease, primarily in patients with primary hyperparathyroidism.

Radiopharmaceuticals (Tracers) for Single-Photon Imaging of the Parathyroid Glands

Sestamibi

Technetium-99m-radiolabeled methoxyisobutyl isonitrile (hereafter referred to as "sestamibi" or "MIBI") has long been utilized for the scintigraphic evaluation of parathyroid abnormalities and is currently the standard radiopharmaceutical employed for this purpose. Delivery of MIBI occurs in proportion to blood flow, and thus, it is distributed to virtually all glandular tissue in the head and neck following intravenous administration, to include salivary, thyroid, and parathyroid glands. Uptake in both parathyroid and thyroid glands peaks early (at approximately 5 min) and subsequently declines in normal tissues but plateaus in adenomatous tissues [6]. It is this early, somewhat generalized tissue distribution of MIBI that necessitates the acquisition of additional delayed images in the investigation of parathyroid abnormalities (see below).

The retention of MIBI in neoplastic tissues has contributed most to its utility in the localization of abnormal parathyroid glands. Early studies in cultured cardiomyocytes revealed that MIBI is lipophilic and cationic, and thus passively crosses the cell membrane in a membrane potential-dependent manner and accumulates with negatively charged mitochondria [3]. Therefore, it is not surprising that the sensitivity of MIBI-based parathyroid imaging has been correlated with the relative percentage of mitochondria-rich oxyphil cells within adenomatous parathyroid tissue [13, 21, 35]. The accumulation of MIBI in adenomas—both parathyroid and thyroid—allows for the acquisition of delayed (typically 2–3 h post-radiopharmaceutical injection) scintigraphic imaging and is an integral part of most parathyroid imaging protocols.

For parathyroid imaging, sestamibi is administered intravenously at usual doses of 740–1110 MBq (20–30 mCi), with the so-called early imaging 20–30 min later and delayed imaging at 2–3 h post-injection [57]. Scintigraphic imaging may include any combination of planar, tomographic (single-photon emission tomography, i.e., SPECT), and/or SPECT imaging with concurrently (hybrid) or separately acquired and fused computed tomography (CT), i.e., SPECT-CT. The 99m-technetium radioisotope emits a gamma-ray (photon) with a predominate energy of 140 keV and has a physical half-life of 6 h.

Pertechnetate

Technetium-99m-radiolabeled pertechnetate ($Tc\text{-}NaO_4$, hereafter referred to as "pertechnetate") has been used for many years for thyroid imaging, particularly in children for whom its dosimetry characteristics make it highly valuable as compared to the radioactive iodides [56]. In the setting of parathyroid imaging, pertechnetate is used to provide a map of thyroid uptake such that images acquired early after sestamibi administration can be corrected for thyroid uptake (i.e., a map of the thyroid can be "subtracted" from the early MIBI image which contains both thyroid and parathyroid uptake). Administered activities of pertechnetate are typically on the order of 74–370 MBq (2–10 mCi), with planar images of the thyroid gland obtained 15–20 min after intravenous pertechnetate administration [58]. Advantages of this method will be addressed below.

Sodium Iodide

Lastly, very small administered activities of the sodium iodide salts (most often 7–15 MBq iodine-123 sodium iodide (200–400 microCuries)) may be used in a manner similar to pertechnetate to provide a map of the thyroid gland for the purposes of subtraction. While this radiopharmaceutical is highly specific for the thyroid and provides good image quality, it is significantly more expensive than pertechnetate and results in a higher radiation dose to the thyroid gland [56].

Planar Versus Tomographic Single-Photon Imaging Protocols

For the purposes of a discussion of the evidence regarding the utility and accuracy of SPECT and SPECT-CT in parathyroid adenoma diagnosis, it is necessary to outline briefly the commonest protocols used for imaging of these glands, as much of the research may at first seem incongruous due to variability in imaging protocols. Historically, the parathyroid glands were evaluated using a planar three-view (anterior, right anterior oblique (RAO), and left anterior oblique (LAO)) scintigraphic protocol, with a head and neck field of view extending from the orbits through the level of the lower mediastinum or aortic arch. Planar images obtained shortly after sestamibi administration—"early images"—were compared with planar images obtained after a 1–3-h delay—"delayed images." In this way, parathyroid adenomas, which are known to retain sestamibi to a greater extent than normal parathyroid glands or thyroid glands, were diagnosed based on the focal retention of sestamibi activity on delayed images typically in an area that showed some sort of asymmetry or focality on early images (see Fig. 12.1a). This dual-phase planar protocol has been widely used and remains the mainstay in many centers. However, with the advent and widespread availability of tomographic (SPECT) imaging, scintigraphy protocols more frequently involve the addition of SPECT or SPECT-CT imaging to planar imaging in at least one imaging time point. Therefore, it is common presently to see, clinically and in the literature, dual-phase protocols involving both planar and SPECT or SPECT-CT imaging of the head and neck. As they represent the current standard of care, the use of dual-phase protocols is implicit in the following discussions with the type of imaging (functional planar versus functional tomographic with or without anatomic information) of primary concern.

Less common, though growing in use particularly in Europe, is the use of a dual-tracer technique (using either pertechnetate or radioiodine) which allows for the explicit consideration and subtraction of thyroid uptake from the early planar sestamibi scan. Evidence regarding the advantages and disadvantages of these dual-tracer and subtraction techniques is considered in the discussions below.

Planar Scintigraphy

The planar scintigraphy technique is the simplest and easiest protocol for the detection of parathyroid disease. Planar images may be obtained using a standard low energy parallel hole collimator, or preferably via pinhole collimation which provides magnification of small structures [30]. When optimized with pinhole imaging, the dual-phase planar technique may be up to 82–91 % sensitive for the detection of adenoma and hyperplasia [23]. When compared to tomographic (SPECT) imaging, the planar protocol is logistically more robust as it does not require patients to remain still for long periods without a break, and it can be performed with even the most basic Anger camera. In addition, planar images can be obtained in patients for whom SPECT may be challenging, such as very obese patients and those with severe claustrophobia. For these reasons, it is unlikely that planar imaging will disappear from the standard parathyroid scintigraphy protocol.

However, data obtained over the past decade suggests that dual-phase planar imaging by itself provides inadequate sensitivity for the detection

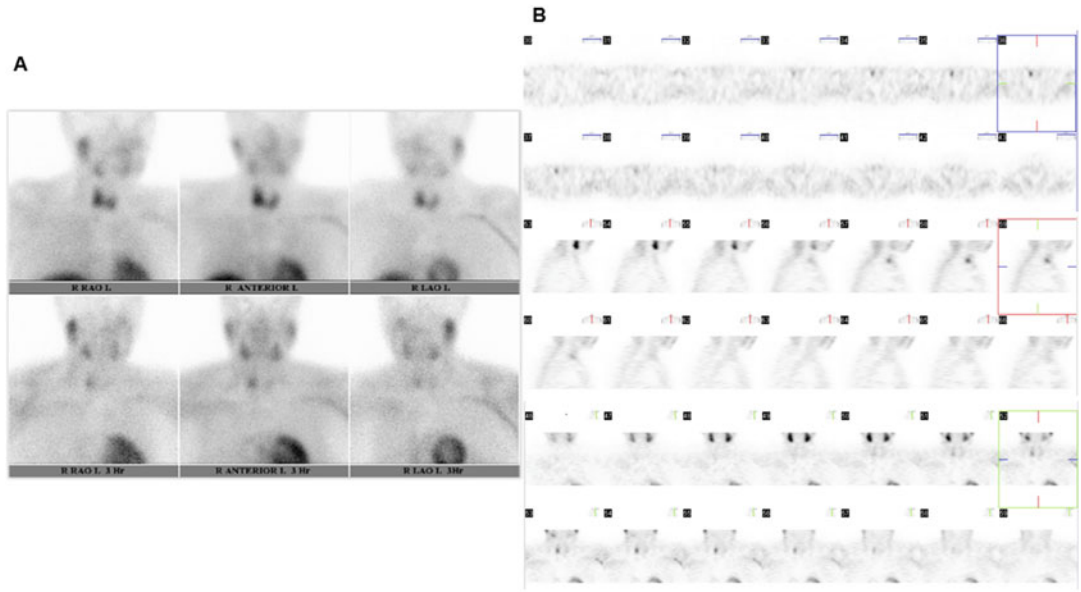

Fig. 12.1 Left inferior parathyroid adenoma. 62-year-old female with 3–4-year history of nephrolithiasis and hypercalcemia. Presented with a total serum calcium of 10.4 mg/dL (normal 8.6–10.4) and parathormone level of 171 pg/mL (normal 14–64). (**a**) Early (*top*) and three-hour delayed (bottom) planar (right anterior oblique—left, anterior—center, and left anterior oblique—right) images were obtained, and revealed focal uptake in the inferior right thyroid bed, which persisted on delayed imaging. (**b**) Delayed SPECT images of the same patient, reconstructed in the axial (top), sagittal (middle), and coronal (bottom) planes, demonstrate the ability of tomographic imaging to identify parathyroid adenoma with high target-to-background ratio. On surgery, parathyroid adenoma was excised

of parathyroid adenomas, even in single-gland disease (see discussion below). Even the maximal sensitivity of planar imaging is compromised in patients with ectopic disease. Thus, imaging with SPECT has become a mainstay of evaluation.

Single-Photon Tomographic Imaging

The availability of multi-head Anger cameras has allowed for the proliferation of SPECT in scintigraphic imaging protocols. By allowing for a tomographic three-dimensional reconstruction of tracer distribution in the head and neck regions, SPECT overcomes the interpretation difficulties related to the superimposition of tracer activity on planar images (see Fig. 12.1b). Thomas et al. [47] demonstrated a sensitivity of dual-phase SPECT of 67 % as compared to 42 % for dual-phase planar imaging, somewhat similar to sensitivities of 62 % and 57 %, respectively, as reported by Lavely and colleagues [31]. Additionally, the use of SPECT increases reader confidence when compared to planar imaging [44].

In that it does not add to patient radiation dose, the primary disadvantage of SPECT as compared to planar scintigraphy is the prolongation of the imaging protocol. In addition, though few, there remain centers with cameras that are not capable of routine tomographic imaging, and in these locations SPECT is simply out of reach.

SPECT-CT

Finally, SPECT-CT is considered by some to be an expensive add-on to SPECT—while the value of tomographic imaging is recognized [10, 31, 39], the additional cost and radiation exposure imposed by hybrid CT or post-acquisition fusion of diagnostic CT images to the functional SPECT information are not uniformly appreciated [4, 22,

36]. Practically, the addition of anatomic information (CT) to functional information (SPECT) can be achieved by using either a hybrid SPECT-CT capable of the consecutive acquisition of SPECT and multi-slice CT in one unit or the software fusion of separately acquired diagnostic CT and SPECT images. In the former, the CT obtained is often done in the absence of intravenous contrast, and kVp and mAs are minimized. Though this serves to limit radiation dose to the patient, the acquisition of diagnostic-quality CT images, even in the absence of intravenous contrast, increases the utility of the combination image for the purposes of surgical planning and intraoperative correlation. In most cases, the current literature examines the diagnostic capabilities of SPECT-CT obtained utilizing a hybrid SPECT-CT camera, and it is generally assumed that post-acquisition fusion SPECT + CT images are similarly valuable though perhaps technically challenging due to the need for high-accuracy software fusion of SPECT and CT images. In many cases, therefore, hybrid SPECT-CT images are obtained and are correlated with diagnostic CT images preoperatively.

There seems to be little doubt that SPECT-CT is superior to planar-only imaging in the diagnosis of parathyroid adenomas [31, 48]. The exact nature of the benefits provided by SPECT-CT over SPECT remains a source of some debate, though it seems clear that SPECT-CT offers improved accuracy in ectopic glands. A recent meta-analysis of 24 articles on scintigraphy for hyperparathyroidism suggests that SPECT-CT has overall better sensitivity and specificity when compared to planar or SPECT-only protocols [4]. In their study comparing single-photon imaging protocols, Lavely et al. [31] identified early SPECT-CT imaging in concert with any (three-view planar, SPECT, or SPECT-CT) delayed imaging as the most sensitive protocol for the accurate identification of parathyroid adenomas. Since then, numerous studies have sought to identify the incremental value of the addition of CT to SPECT, with somewhat mixed results. In their subset of patients with hyperparathyroidism, Bural et al. [14] suggested that SPECT-CT allowed for more accurate parathyroid adenoma localization on a per-patient basis than did SPECT (sensitivities of 97 % for SPECT-CT and 61 % for SPECT-only). Furthermore, the addition of CT to SPECT has been shown to increase reader confidence, thereby decreasing the number of false-positive SPECT findings (see Fig. 12.2). In a retrospective analysis of SPECT-CT images from 50 patients undergoing preoperative parathyroid localization, Mandal et al. [33] suggest that early-only MIBI SPECT-CT is sufficiently sensitive and specific, and that delayed-phase images may be unnecessary. In large part, the gains seen with SPECT-CT over SPECT relate partially to improvements in the localization

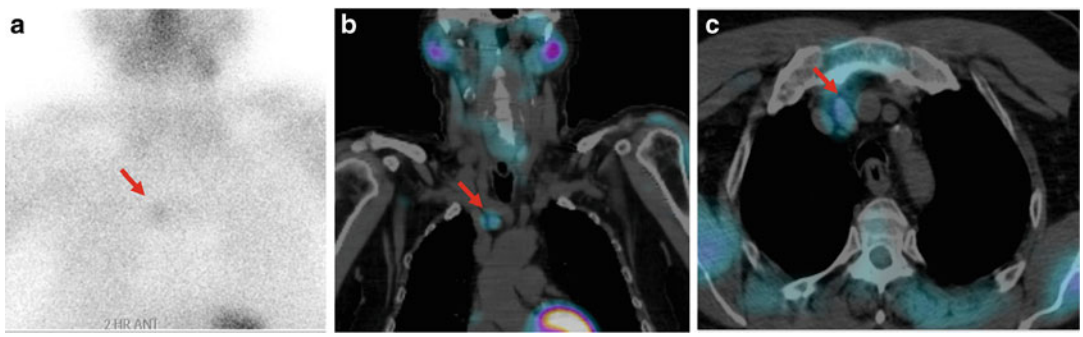

Fig. 12.2 False-positive sestamibi uptake within mediastinal brown fat. 80-year-old female presented with a history of hypercalcemia and intact PTH of 93.1 pg/mL (normal 12.0–88.0). No focal MIBI was seen in the neck, but focal retention was noted in the chest on functional imaging (*right*). SPECT-CT fused image (*left*) reveals this focus to be within brown fat within the mediastinum

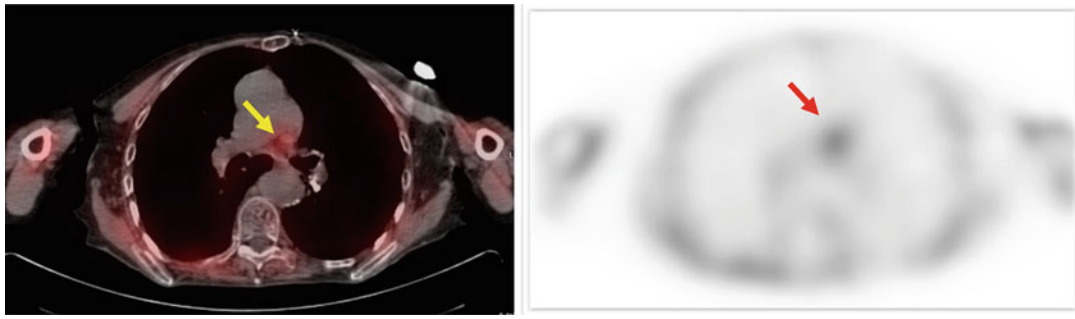

Fig. 12.3 Ectopic (superior mediastinal) parathyroid adenoma. 69-year-old male with total serum calcium of 11.5 mg/dL (normal 8.6–10.2) and parathormone level of 132 pg/mL (normal 14–64). (**a**) Delayed anterior planar MIBI image reveals focal activity in the anterior chest. Hybrid SPECT-CT coronal (**b**) and axial (**c**) views confirmed focal uptake in a 2 cm soft-tissue nodule in the anterior superior mediastinum. On surgery, a 2.5 cm parathyroid adenoma was excised

of ectopic versus eutopic glands and partially to increased reader confidence [20, 42] (see Fig. 12.3). A recent study [2] has suggested that the method of imaging reconstruction utilized in SPECT-CT versus that performed with SPECT-only scanning may also contribute to the superior performance of the former; further study in this area may be of benefit, as it may have important clinical implications for centers with the capability to perform SPECT but not SPECT-CT.

Single-Tracer Versus Dual-Tracer Imaging Protocols

It is worth noting at the outset that dual-tracer protocols impart a higher radiation dose to patients than do protocols that utilize MIBI only. Members of the medical imaging community consider this incremental increase in radiation dose to have a high risk-benefit profile, and therefore, it is not typically considered to be prohibitive. For further discussions of radiation doses related to scintigraphic imaging, please see Chap. 41.

In an unselected representative patient population, the addition of planar thyroid imaging with subtraction to a dual-phase MIBI imaging protocol has been shown to increase specificity for parathyroid adenoma detection to over 94 % [12]. In a small study comparing dual-tracer techniques to four different single-tracer (MIBI) protocols, Tunninen et al. [49] concluded that the dual-tracer technique utilizing I-123 sodium iodide was superior to MIBI protocols employing either pinhole planar or SPECT-CT methodologies. Interestingly, recent work by Heiba and colleagues [27] compared dual-tracer dual-phase pinhole planar imaging to various protocols (including single-tracer MIBI imaging) with and without SPECT-CT. Their findings suggest that dual-tracer pinhole planar imaging is equivalent to dual-phase single-tracer pinhole imaging, but that the addition of SPECT-CT to dual-tracer pinhole planar protocol yields the highest performance with an accuracy of over 95 %. Neumann and colleagues [36] performed thyroid subtraction SPECT, and evaluated its performance with and without concomitant CT, concluding that the addition of CT to the SPECT protocol significantly improved specificity on a per-lesion basis (96 % for SPECT-CT as compared to 48 % for SPECT-only), with both having sensitivities of about 70 %. These studies suggest that, while dual-tracer methodologies are valuable particularly in patients with thyroid disease, they cannot supplant the benefit of CT correlation with SPECT. Further evaluation of these options may be valuable, as even low-dose CT adds, on average, 1–2 mSv to the approximately 8 mSv effective radiation dose of a planar + SPECT sestamibi protocol [as a comparison, a dose of pertechnetate for thyroid imaging adds up to 2 mSv to the dose of the same protocol, and a typical dose of I-123 NaI would add ~4 mSv to a sestamibi parathyroid imaging study] [43, 57].

Performance of Single-Photon Imaging in Multi-Glandular and Hyperplastic Disease

The literature clearly documents that the accuracy of scintigraphic imaging suffers in the setting of multi-glandular disease. Katz et al. [29] demonstrated that study sensitivity decreased to 23 % in patients with pathologically proven multi-gland disease as compared to a sensitivity of 70 % in solitary adenomas; in their study, none of the bilaterally diseased glands among 15 patients in their cohort were correctly localized on preoperative planar MIBI (an undisclosed number of patients also underwent SPECT imaging). In an analysis of just over 400 patients, Chiu et al. [16] found that patients with multi-gland disease were more likely to have non-localizing MIBI scans, frequently revealing no focal uptake at all. Similarly, a multicenter study examining primary hyperparathyroid patients with failed surgery revealed that over half of patients with persistent postoperative hyperparathyroidism suffered from multi-gland disease not localized on the combination of ultrasound and MIBI scintigraphy [11]. Notably, using a dual-tracer dual-phase protocol, Guerin et al. [24] showed preoperative parathyroid scintigraphy to be localizing in as many as 61 % of patients with multi-glandular disease.

Special Populations

Secondary and Tertiary Hyperparathyroidism

In patients with renal failure resulting in secondary and/or tertiary hyperparathyroidism, typically more than one parathyroid gland becomes hyperfunctional. In an analysis of 166 patients with secondary and tertiary hyperparathyroidism, Cruz de Andrade et al. [19] demonstrated an overall sensitivity of 91 % for MIBI scintigraphy, with scintigraphy correctly localizing only 26 % of ectopic glands but virtually all eutopic glands; notably, this retrospective study included scintigraphic image reports from numerous sites, and the utilization of planar versus SPECT or SPECT-CT is not clear. Likewise, in additional studies of patients with secondary hyperparathyroidism related to renal failure, preoperative dual-tracer dual-phase scintigraphic imaging and MIBI single-tracer dual-phase SPECT-CT imaging have been shown to be valuable in accurately localizing hyperfunctioning parathyroid glands [17, 53].

Overall, as these patients tend to represent a small minority of patients presenting for parathyroid scintigraphy, thus far there is inconclusive data regarding the accuracy of scintigraphy in this patient population and larger studies in this patient population are needed.

Known or Suspected Thyroid Adenoma or Thyroid Disease

Intuitively, it is patients with known or suspected thyroid disease in whom the dual-tracer and SPECT-CT protocols may be most beneficial. A prospective study of 50 patients with primary hyperparathyroidism and nodular goiter on physical exam demonstrated superiority of SPECT-CT as compared to SPECT and planar imaging in a dual-phase single-tracer protocol, with accuracies of 85 %, 75 %, and 65 %, respectively [8]. Utilizing a novel protocol of both dynamic planar imaging and subtraction dual-tracer tomography, Berner et al. [12] demonstrated per-lesion sensitivity, specificity, and accuracy of 71 %, 94 %, and 76 %, respectively. This was superior to ultrasound, which had sensitivity, specificity, and accuracy of 60 %, 72 %, and 62 % in this same patient population; similar results were reported by Markovic and colleagues [34]. It should be noted, however, that while this represents very good performance of scintigraphy in these patients, these groups utilized software developed locally for the subtraction and quantification of relative parathyroid uptake on planar images; such software is not widely available or accessible for most imaging centers and clinicians. Importantly, Pata et al. [38] showed that SPECT-CT provides sensitivity and specificity of 94 % and 93 % in side localization in patients

with nodular goiter, and that it decreased operating time. Even in the absence of quantitation, the availability of contemporaneous thyroid images is highly desirable for accurate preoperative findings in patients with known thyroid abnormalities as defined by ultrasound [18]. Thus, the use of thyroid imaging in concert with dual-phase MIBI parathyroid imaging is desirable in patients with known or suspected thyroid disease.

Postsurgical Recurrent Hyperparathyroidism

Even after successful parathyroidectomy (as defined by criteria with a post-excisional drop in intact parathormone (iPTH) level of >50 %), some patients will go on to have recurrent hyperparathyroidism. In these patients, the rate of ectopic parathyroid adenoma is disproportionately high as compared to the general population of those with hyperparathyroidism. In small studies, MIBI scintigraphy has demonstrated poor performance in the re-operative setting, with sensitivity as low as 33 % for dual-phase MIBI SPECT [52]. In contrast, both sensitivity and specificity of scintigraphy in this subpopulation of patients were shown to be higher when SPECT and/or SPECT-CT are utilized in addition to planar imaging with MIBI by Lu and colleagues [32], who described a small series of patients with recurrent hyperparathyroidism in whom MIBI SPECT-CT successfully guided mediastinal parathyroidectomy.

Comparison and Correlation with Other Imaging Modalities

Ultrasound

Guidelines by the Society of Nuclear Medicine and Molecular Imaging (SNMMI) as well as the American Association of Clinical Endocrinologists (AACE) and the European Association of Nuclear Medicine (EANM) uniformly recognize the complementary role of ultrasound and scintigraphy in preoperative localization and surgical planning [57, 59, 60]. Numerous retrospective studies have suggested that the use of neck ultrasound plus scintigraphy is superior to either imaging method alone in the preoperative diagnosis of parathyroid adenomas [25, 26, 40]. Some studies have suggested that, despite the inter-operator variability in ultrasound performance, there is some evidence that ultrasound in the hands of highly skilled practitioners may reliably detect culprit parathyroid glands as readily as dual-phase MIBI and dual-tracer planar imaging [45, 50, 51]. Conversely, when SPECT-CT is available, the data is less compelling regarding the additional utility of ultrasound above that of dual-phase SPECT-CT in the localization of solitary parathyroid adenomas and minimization of surgical extent [46]. In patients found to have ectopic adenomas on surgical exploration, planar and/or tomographic scintigraphy successfully identified and localized the diseased gland even in ultrasound-negative patients [41]. While ultrasound infrequently identifies adenomas not seen on scintigraphy, ultrasound can identify thyroid abnormalities and thereby provide vital information for scintigraphic correlation or identification of patients in whom concurrent thyroid imaging should be performed (i.e., patients for whom a dual-tracer protocol should be considered) [37].

Positron Emission Tomography, PET-CT, and Four-Dimensional CT

In the field of parathyroid imaging, positron emission tomography (PET), PET-CT, and four-dimensional CT (4DCT) represent emerging methodologies. To date, only small studies have compared PET or PET-CT to dual-phase planar + SPECT (or SPECT-CT) imaging and have suggested utility of PET using a methionine tracer (MET-PET) for localization of adenomas in SPECT-negative patients or those with recurrent disease [7]. In the general population of patients with primary hyperparathyroidism, MET-PET has thus far performed less well than

MIBI SPECT [28]. This conflicts somewhat with work by Tang and colleagues [9], who demonstrated virtual equivalence of the two modalities in their evaluation of 32 patients, with MET PET-CT and MIBI SPECT-CT having sensitivities of 92 % and 95 % for adenoma and 68 % and 59 % for hyperplasia, respectively. As with MET PET, the performance of 4DCT as compared to MIBI scintigraphy necessitates further study. In a case series of 38 patients, Suh et al. [54] retrospectively analyzed imaging data of patients who had undergone high-resolution ultrasound, 4DCT, and dual-phase MIBI SPECT-CT, and found 4DCT to be of higher specificity than MIBI and US imaging (96 %, 90 %, and 87 %, respectively). In the re-operative setting, 4DCT may allow for shorter operating times in patients with negative MIBI imaging [15]. Currently, PET and 4DCT protocols are higher in both real and radiation exposure costs for patients than MIBI-based scintigraphy [1]. In addition, the search for high-quality, widely distributable PET tracers continues [7]. For further discussion of 4DCT and PET-CT imaging in the diagnosis of parathyroid disease, please see Chaps. 14 and 15, respectively.

Summary

The successful preoperative localization of diseased parathyroid glands using scintigraphy has substantially impacted the surgical approach and patient experience of hyperparathyroidism clinical management [5]. Still, the performance of scintigraphy suffers in patients with multi-gland disease/hyperplasia and in the re-operative setting. Clearly, tomographic protocols have distinct advantages over planar-only protocols, though the "best" protocol (in terms of SPECT early versus SPECT late) remains to be determined. In addition, the use of dual-tracer protocols provides distinct benefits in patients with suspected thyroid disease while imparting only a small additional radiation dose. It is likely that single photon-based parathyroid scintigraphy will continue to play a vital role in the diagnostic evaluation of patients with hyperparathyroidism for many years to come.

Society Guidelines

Society of Nuclear Medicine and Molecular Imaging (SNMMI) Procedure Standard:

Greenspan BS, Dillehay G, Intenzo C, Lavely WC, O'Doherty M, Palestro CJ, Scheve W, Stabin MG, Sylvestros D, Tulchinsky M. SNM practice guideline for parathyroid scintigraphy 4.0. *J Nucl Med Technol*. 2012; 40(2): 111–118. PMID: 22454462.

European Association of Nuclear Medicine (EANM) Guideline:

Hindié E, Ugur O, Fuster D, O'Doherty M, Grassetto G, Ureña P, Kettle A, Gulec SA, Pons F, Rubello D. 2009 EANM parathyroid guidelines. *Eur J Nucl Med Mol Imaging*. 2009; 36(7): 1201–1216 [59].

American College of Radiology (ACR) Practice Parameter:

Allen TW, Bruno MA, Gelfand MJ, Grant FD, Metter DF, Sharp SE. ACR-SPR practice parameter for the performance of parathyroid scintigraphy [Internet]. Reston, VA: American College of Radiology; 2014 (Resolution 32) [cited 2015 Jun 8]. Available from: http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/Parathyroid_Scintigraphy.pdf.

Best Practices: N/A

Expert Opinion

Dual-phase sestamibi scintigraphy is currently the imaging method of choice for the evaluation of most patients with suspected parathyroid disease, and has proven to be both robust and reproducible for the identification of solitary adenomas in patients with primary hyperparathyroidism. Dual-tracer subtraction techniques may be particularly efficacious in patients with a history of or suspected thyroid disease. However, SPECT-CT obtained at either time point during a dual-phase sestamibi protocol likely offers similar benefits to the dual-tracer techniques with regard to thyroid-versus-parathyroid localization, with the added benefit of CT-based anatomic localization for surgical planning.

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Ultrasound

13

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Contents

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Parathyroid Ultrasound Localization

The general background of ultrasonography has been addressed elsewhere in this book and will not be repeated in detail. Briefly, the ultrasound instrument should be set at higher frequency to maximize resolution (>10 mHz). US localization of parathyroid glands should then be approached in a systematic manner. One popular approach is to initiate the scan at the level of the right subclavian between the carotid and larynx with the transducer in the transverse position, proceeding in the cephalic direction to the level of the superior pole of the thyroid gland. This approach not only searches for a parathyroid adenoma but also evaluates the thyroid gland looking for nodules and other abnormalities. This process is repeated in the left central neck again moving the transducer from the left subclavian to the superior pole of the left lobe between the larynx and the carotid. The superior parathyroid glands are located posterior to the mid-thyroid lobes. Inferior parathyroid glands are most commonly caudal to the inferior thyroid pole. Any suspected adenoma should then be evaluated with the transducer in the sagittal plane. Normal parathyroid glands are typically less than 40 mg and are extremely difficult to characterize by ultrasound. Ultrasound characteristics suggestive of an adenoma include hypoechogenicity and increased blood flow to the pole rather than to the central

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area as seen in lymph nodes. There also may be increased blood flow to the parathyroid capsule or adjacent thyroid tissue [1]. If there is any uncertainty as to whether or not a nodule is a parathyroid adenoma, fine-needle aspiration biopsy with saline washout and measurement for PTH will establish the diagnosis. This is especially helpful in the rare circumstance of an intrathyroidal parathyroid adenoma that occurs approximately 6 % of the time [2]. In a large meta-analysis of 20,000 patients, primary hyperparathyroidism results from a single adenoma in approximately 88.9 % of cases, double adenoma occurs in 4.1 %, and four-gland disease/hypertrophy in 5.8 % [3]. It has recently been shown that the ability to detect a parathyroid adenoma by US and sestamibi may be related to the severity of the disease [4].

US is almost always used in conjunction with other imaging modalities. The optimal combination of preoperative imaging modalities to this point is unknown. The choice of which imaging modality to employ and in what order is highly dependent upon institutional expertise and available instrumentation. US is routinely performed as an initial study because it is noninvasive, relatively inexpensive, and widely available. However, US is extremely operative dependent and the reported sensitivity of US-identified parathyroid adenoma ranges from 72 to 89 % [5–7]. In one study of 77 consecutive patients with a diagnosis of PHPT who had a preoperative US performed, the correct quadrant was identified in 78 % of patients and the correct side identified in 95 % of the patients [5]. In a prospective study of 56 patients with PHPT, of those with a solitary lesion, the sensitivity of MIBI was 97 % and US 74 % [8]. A retrospective study of 61 PHPT patients with preoperative sestamibi scan and US showed correct localization in 88 % and 77 %, respectively [9]. A recent comparison of US and MIBI showed that US and MIBI successfully identified adenoma in 77 % and 88.5 %, respectively. When both were concordant, 100 % of lesions were correctly identified [9].

Ultrasonography is less effective in localizing parathyroid adenomas in secondary hyperparathyroidism from renal failure or MEN syndromes and in reoperation for persistent/recurrent disease. In a study of 166 patients with HPT as a consequence of renal disease, MIBI and US together failed to detect 61.5 % of ectopic glands [10]. In 288 patients that required a reoperation for persistent hyperparathyroidism sestamibi provided the best results with 67 % true-positive and no false-positive results. US only had a 48 % true-positive result and 21 % false-positive [11]. In a similar study of 102 patients who underwent reoperation for persistent disease, sestamibi scans detected 67 % and US 57 % [12]. US also has a very limited role in identifying ectopic parathyroid glands and is rarely successful. The combination of US and sestamibi scan has been shown to increase diagnostic accuracy [13] and the combination of the two has become first-line in parathyroid localization at many institutions [14].

The diagnostic accuracy of ultrasonography to localize an adenoma in some studies has been shown to be reduced in the presence of thyroid nodules [15] and hyperparathyroidism secondary to renal insufficiency [16]. This was not universally true. The sensitivity was similar between US coupled with FNA and PTH washout (90 %) compared with nuclear medicine imaging of patients without (89 %) and with (74.3 %) thyroid pathology [17]. Well-trained surgeons and endocrinologist have been shown to have similar accuracy rates as compared to those achieved by sestamibi scan or when a radiologist performs the US. In a study of 226 patients with primary hyperparathyroidism, surgeon-performed US correctly identified the parathyroid adenoma in 77 % of cases compared with 57 % correctly identified by sestamibi [18]. In a large series of 916 evaluable patients, surgeon-performed US correctly localized parathyroid adenoma in 80 % of cases compared with 74 % with sestamibi. 156 patients with primary hyperparathyroidism from a single adenoma were evaluated by US performed by an endocrinologist and radiologist. US performed by an endocrinologist identified 12 % of the adenomas missed by US performed by a radiologist [19].

It is important to note however that there is a wide discrepancy between the resolution of US instrumentation in radiology departments com-

pared with the resolution of less expensive instrumentation often employed in the community. The majority of studies evaluating US localization have been done on high-resolution instruments in well-trained hands.

Parathyroid Ethanol Injection

The procedure for parathyroid ethanol injection (PEI) involves the accurate localization of the parathyroid adenoma, precise placement of the needle tip within the adenoma, and careful injection of ethanol. The amount of ethanol injected varies widely between studies and the optimal volume has not been determined. Up to 2 ml of ETOH was injected in one study [20] and others calculated the volume of the adenoma with administration of 70–100 % of this volume with ethanol [21–23]. This discrepancy may partially explain the wide discrepancy in results from various studies.

Secondary/Tertiary Hyperparathyroidism

Often more than one surgery is required to render tertiary hyperparathyroid and MEN1 patients eucalcemic/hypocalcemic. Reoperation in these patients is considerably longer and the risk of complications is increased. PEI has been used primarily in these patient populations. PEI within a parathyroid adenoma under US guidance was first used to destroy parathyroid parenchyma in secondary hyperparathyroidism and normalize PTH levels in 1985 [24]. The reduction in PTH levels was shown to be rapid, occurring within a median of 24 h in seven patients with PHPT injected on 3 consecutive days [25].

In a large study of 321 hemodialysis patients with secondary hyperparathyroidism, PEI reduced calcium from 10.7 ± 0.8 to 10.1 ± .5 mg/dl in 62 % of patients. Success was primarily dependent upon the number of identified hyperplastic glands [23]. 39 patients with tertiary HPT were prospectively followed after either surgery (17) or PEI (22). In 11 of 22 patients, a greater than 30 % reduction in PTH level was achieved with a mean of 1.8 injections. However, no significant reduction was achieved in 11 patients even after a mean of 2.5 injections and these patients required parathyroidectomy. Importantly, four patients developed recurrent laryngeal nerve palsy, two of which were permanent. The authors felt that the outcome was poor compared with parathyroidectomy and could not recommend the procedure in this patient population [26]. In another study, 27 patients underwent 63 ethanol injections with normal calcium and PTH levels obtained in 15 patients. However 4 of the 15 "cured" patients had recurrence after 1–2 years of follow-up. No major complications were observed [27]. In a recent study, 41 PEI were performed in 22 MEN1 patients and the mean calcium level went from 10.6 to 9.5 mg/dl. All but one patient had a decrease in serum calcium after PEI; however, 50 % of the patients required additional PEI [28]. The experience at Mayo Clinic with PEI in MEN1 patients with recurrent HPT from 2007 to 2013 was recently reported [28]. Thirty-seven patients were studied. 80 PEI were performed with 123 ethanol injections. Calcium levels went from 10.7 mg/dl ± 0.57 before injection to 9.6 mg/dl ± 0.76 post-injection. Normocalcemia was achieved in 73 % of patients and hypocalcemia in 8.1 %. Transient hoarseness occurred in four patients, but there were no lasting complications.

Primary Hyperparathyroidism

Surgery is most commonly utilized for the treatment of PHPT, but some patients are at a high surgical risk because of previous surgical attempts at resection, and medical comorbidities, or they refuse the procedure. Several investigators have examined the utility of PEI in the treatment of PHPT. Thirteen PHPT patients underwent PEI and were followed for up to 49 months. Seven patients had complete normalization of PTH levels. Four patients had normalization of calcium levels but incomplete PTH response. PEI failed in two patients. No major complications were reported [29]. PEI has also been employed

to partially ablate a single remaining adenoma. This was part of a study of 33 patients with PHPT in whom it was felt that reoperative surgery would be technically unsafe, had exclusive medical comorbidities, or had a single remaining adenoma who underwent PEI. There were no long-term complications; however two patients had temporary recurrent laryngeal nerve injury and four had temporary hypocalcemia. 34 % of attempted complete ablations were eucalcemic after 16 months whereas only 2 of 7 partial ablations were successful [30].

Other Methods of Ablation

Several other novel treatment modalities for hyperparathyroidism have also been examined. The use of high-intensity focused US was examined in four patients with primary hyperparathyroidism. Serum parathyroid levels decreased in all patients and normalized in two, and serum calcium levels normalized in three patients [31]. Microwave ablation was retrospectively studied in 11 patients with recurrent or persistent secondary hyperparathyroidism after parathyroidectomy. PTH levels decreased from 1570 pg/ml to 287 pg/ml [28].

Summary

- Ultrasound is widely used to identify single parathyroid adenoma, and is often the first-line imaging test.
- The sensitivity of US imaging varies widely between institutions, probably reflecting differences in instrumentation and experience.
- Ultrasound is much less effective in identifying multiple adenomas/hyperplastic glands in secondary hyperparathyroidism, presence of thyroid pathology, and ectopic adenomas.
- Concordant ultrasound and sestamibi results are extremely accurate in localization.
- Parathyroid ethanol injection is relatively safe with few long-term complications; however permanent recurrent laryngeal nerve palsy has been reported.
- Multiple injections are often required to achieve normal parathyroid and calcium levels.
- The success rate for ethanol injection varies widely, particularly in the

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion

US should be the first imaging modality used in attempts to localize parathyroid adenoma(s). It is safe, relatively inexpensive, and highly specific. A second imaging modality, traditionally MIBI scanning, is routinely performed; however other imaging modalities such as CT, 4D CT, or MRI may also be employed. When ultrasound and MIBI scanning are concordant, accuracy approaches 100 %. Ultrasonography is highly dependent upon the ultrasonographer and the instrument employed; therefore institutions may not achieve results reported in the literature.

PEI is generally safe and effective in select patients that are not surgical candidates by choice, risk of reoperation, or medical comorbidities. PEI as a first-line therapy for PHPT has not been widely accepted. PEI should only be performed by experienced ultrasonographers to achieve optimal results and limit complications.

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CT Imaging for Parathyroid Disease

14

Ryan T. Fitzgerald

Contents

Introduction

Recent years have seen a transition from exploratory surgery for parathyroid disease to targeted or minimally invasive procedures that may be amenable to being performed on an outpatient basis and confer decreased morbidity relative to universal bilateral exploratory surgeries. Minimally invasive parathyroidectomy (MIP) facilitated by imaging localization of single-gland parathyroid disease has been reported to be successful in up to 97 % of cases [1]. Localization for parathyroid disease has traditionally been accomplished by nuclear scintigraphy (MIBI) and ultrasound, and many surgeons rely on congruent two-modality localization prior to performing MIP. In 2006, Rodgers et al. published their initial experience with computed tomography (CT) in patients with primary hyperparathyroidism reporting that CT provides improved sensitivity relative to scintigraphy and ultrasound for precise localization of parathyroid adenomas [2]. Since that time, CT has been adopted in an expanding number of practices, often as a second-line tool for patients whose lesions do not localize with scintigraphy or ultrasound and now, at some institutions, as a first-line modality for localization in patients with primary hyperparathyroidism [3]. Some groups have even called for the abandonment of routine sestamibi single-positron emission computed tomography

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(SPECT) in favor of low-dose multi-phase CT as the imaging modality of choice for preoperative localization of adenomas [4].

CT for parathyroid imaging is commonly referred to as "multi-phase" or "4D-CT" in reference to the addition of a time dimension to the static 3-dimensional dataset acquired by a typical single-phase CT scan. A variety of imaging strategies have been employed, but at most institutions 4DCT entails a pre-contrast acquisition followed by at least two contrast-enhanced acquisitions at different time points (Fig. 14.1). Many groups now employ a three-phase technique (pre-contrast, early contrast-enhanced, and delayed contrast-enhanced acquisitions) whereas other groups have used a four-phase technique and some have even argued that a single arterial phase acquisition provides sufficient diagnostic accuracy for localization of parathyroid adenomas [5]. As of 2015, the majority of study authors maintain that a three-phase protocol is ideal for not only providing optimal sensitivity but also maximizing the diagnostic confidence with which a parathyroid lesion can be reported. Further refinement of the 4DCT technique may occur as the parathyroid imaging community accrues more data regarding the test characteristics of various protocols.

The applicability of 4DCT for detection and localization of parathyroid disease is based on multiple factors including (1) the differential attenuation of parathyroid tissue and thyroid parenchyma on pre-contrast imaging, (2) the differential contrast enhancement and washout of parathyroid lesions versus adenoma mimics such as lymph nodes, (3) improved spatial resolution of CT relative to scintigraphy, (4) improved visualization of deep and ectopic lesions relative to ultrasound, and (5) superior visualization and spatial discrimination of structures within and adjacent to the planned surgical approach such as blood vessels.

On non-enhanced imaging, parathyroid adenomas are characteristically less dense than iodine-rich thyroid parenchyma, a feature that can be helpful in distinguishing orthotopic parathyroid lesions from exophytic thyroid nodules. Secondly, most parathyroid adenomas, over 92 % in one study, show hyper-enhancement on (near-equivalent enhancement to nearby arteries) arterial phase CT imaging [6]. Delayed or venous-phase imaging characteristically reveals a decrease in the density of parathyroid lesions relative to the arterial phase acquisition. Such a pattern allows differentiation of parathyroid lesions from lymph nodes, which characteristically display a gradual accrual of contrast and thus show a stepwise increase in attenuation from pre-contrast to arterial and delayed venous-phase imaging (Fig. 14.2).

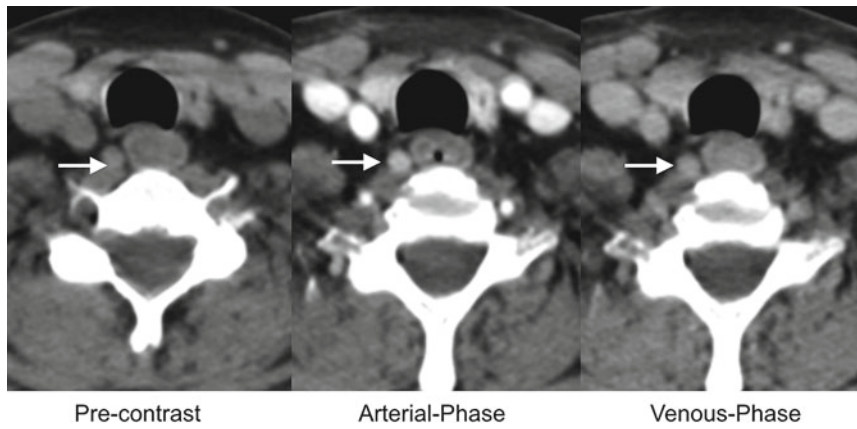

Fig. 14.1 Non-enhanced, arterial, and venous-phase (*left to right*) axial CT images from a 4DCT in a patient with primary hyperparathyroidism shows an ovoid parathyroid adenoma posterior to the right tracheoesophageal groove that measures lower density that thyroid parenchyma on the non-enhanced scan (50 Hounsfield units [HU]), avid enhancement on arterial phase (middle-122 HU), and subsequent contrast washout with venous-phase density of 84 HU

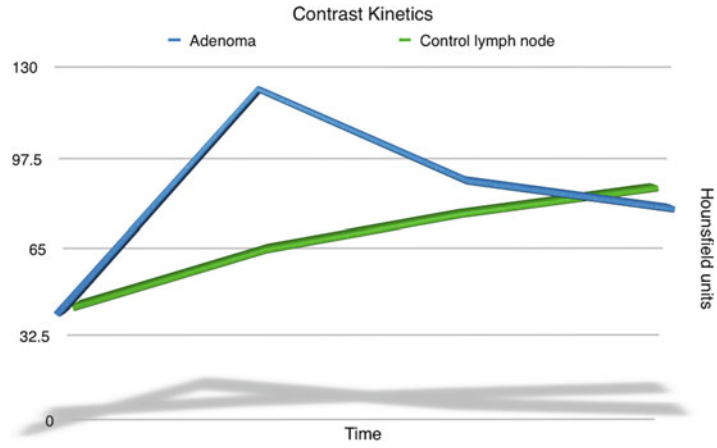

Fig. 14.2 Graph of measured density (*y*-axis) over time (*x*-axis) for parathyroid tissue (*blue*) and a cervical lymph node (*green*) demonstrates the differential enhancement kinetics displayed by these tissues, with parathyroid showing early peak and subsequent washout and lymph nodes displaying continued accumulation of contrast throughout the scan

Variability of the enhancement characteristics of parathyroid lesions (including both adenomas and hyperplastic glands) prompted Bahl et al. to develop a categorization scheme based on attenuation of a candidate lesion relative to the thyroid parenchyma. Type A lesions are higher in attenuation than the thyroid in the arterial phase (20 % of parathyroid lesions); type B lesions are not higher in attenuation than thyroid in the arterial phase but lower on the delayed phase (57 % of lesions); type C lesions are neither higher in attenuation than thyroid in the arterial phase nor lower in the delayed phase (22 %) [7]. Such differences in the enhancement characteristics demonstrate the value of a multi-phase examination including at least three phases. In particular, for type C lesions which are not distinguishable from thyroid parenchyma on either the arterial or delayed-phase acquisitions, a pre-contrast examination serves as the only reliable mean by which to verify that a candidate lesion is indeed of parathyroid origin.

Patient Selection

Practice patterns of individual surgeons and at different institutions regarding the choice of localization modality vary widely; however sestamibi-based imaging (MIBI) and ultrasound remain the most widely used techniques. Many surgeons rely on congruent localization by two different modalities prior to MIP. The role of CT in the preoperative imaging scheme is not fully established due to its relatively recent introduction; however, CT has gained a foothold at several institutions and a complementary localization technique, particularly for patients with negative US and/or MIBI exams. Given the now established superiority of CT to US and MIBI imaging in terms of sensitivity and positive predictive value for adenoma localization (discussed in "Test Characteristic" section) the use of CT may continue to expand in the coming years.

Comparing CT to other well-established parathyroid imaging modalities, US has several benefits including the ease of performing "in-office" exams and lack of any ionizing radiation. Ultrasound is a heavily operator-dependent modality that therefore performs optimally in the hands of an experienced, sub-specialized operator and relatively poorly when conducted by an operator with less experience or by an individual who is unfamiliar with US imaging of the parathyroid glands. Further, US is limited in its ability to detect lesions in ectopic or posterior orthotopic locations due to limited depth of penetration and obscuration of tissues deep to air-filled structures such as the esophagus and trachea. Limitations of MIBI include the nonspecific nature of sestamibi, which is taken up my mitochondria-rich cells regardless of whether or not these cells are located within a parathyroid lesion. As such, the degree of radiotracer uptake correlates with the size and cytological composition of parathyroid lesions, with some lesions being either too small

or oxyphil-poor to be detectable by MIBI [8]. Lower sensitivity of US and MIBI has also been encountered in patients with only mildly elevated PTH and calcium and in obese patients [9]. Lesion size and volume have been shown to be strong independent predictors of successful localization of parathyroid adenomas by both US and MIBI, with decreased ability of these exams to localize smaller lesions (<500 mg) [10, 9]. Not only has 4DCT proven to be efficacious for localization of small parathyroid adenomas, but also allows imaging visualization of normal, non-adenomatous parathyroid glands measuring (typically measuring between 1 and 3 mm in long-axis diameter) in some patients (Fig. 14.3).

Radiation dose of 4DCT is among the chief concerns limiting adoption of the technique. Since the initial description of 4DCT in 2006, many institutions have developed low-dose 4DCT techniques through adjustment of scan parameters and reduction in the number of acquisitions making up the scan. Calculated effective radiation doses for 4DCT have been reported to range from 10.4 (Mahajan 2012) to 28.5 mSv (Hoang 2015) compared to 7.8–12.0 mSv for single-phase planar sestamibi scintigraphy and SPECT [9, 11]. To put these numbers in perspective, the estimated annual background radiation exposure in the US is approximately 3 mSv and the annual average per-capita US radiation dose received from medical procedures is 3.2 mSv (Mahajan 2012). Hoang et al. further explored radiation exposure related to 4DCT by examining organ-specific dose and found that thyroid, salivary glands, and esophagus received the highest dose, whereas with scintigraphy the colon is exposed to the highest radiation dose of any organ in the body. Considering a lifetime incidence of cancer of 46,300 cancers/100,000 population, imaging increases the lifetime incidence of any cancer above baseline by 0.52 % for 4DCT and 0.19 % for scintigraphy. Lung cancer had the highest lifetime attributable risk in both the 4DCT and scintigraphy groups at 98 cancers/100,000 in the 4DCT cohort and 51 for scintigraphy. Lifetime attributable risk for thyroid cancer for 4DCT patients 55 years of age or older was only 3 cancers/100,000 patients despite the relatively high organ-specific dose (Hoang 2015). The higher estimated attributable risk for thyroid cancer in younger patients, 92 cancers/100,00 for female patients at age 25, and 23/100,000 for 25-year-old males warrants consideration of patient age when decided which imaging modality is most appropriate. Any discussion of relative radiation dose between 4DCT and MIBI must also take into consideration the improved sensitivity of the CT technique which translates into fewer initial negative studies and therefore negates the need for additional workup.

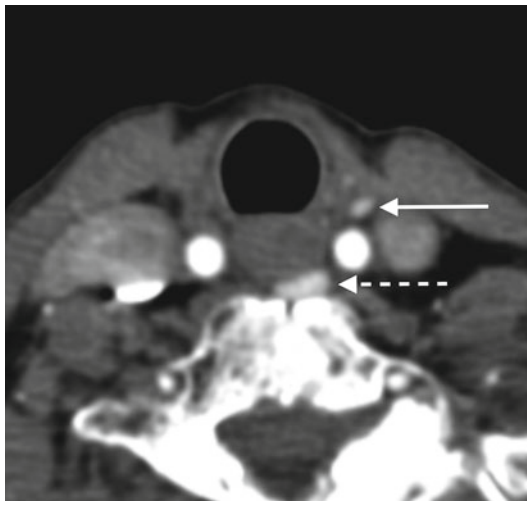

Fig. 14.3 An axial arterial phase 4DCT image demonstrates a left-sided retroesophageal parathyroid adenoma (*dashed arrow*) plus an additional enhancing lesion at the eutopic left superior position thought to represent a normal parathyroid gland

Technique

4DCT for parathyroid disease entails acquisition of imaging data at different time points in order to add physiologic data on top of anatomic and differential tissue contrast data provided by a single-phase CT exam. Techniques for 4DCT vary somewhat from institution, but the most widely utilized protocols today use a pre-contrast study followed by early and delayed contrast-enhanced exams. Such three-phase studies represent a modification of the earlier employed 4DCT technique using a pre-contrast scan followed by three post-contrast scans.

This change came about as a response to concerns over radiation dose and the advent of data showing no clear diagnostic benefit of three post-contrast phases. Timing of the post-contrast acquisitions varies, but most institutions using 4DCT have reported a 25-s or 30-s delay from the beginning of contrast administration to the initiation of the first post-contrast scan followed by an additional scan at 80–90 s. Commonly reported contrast agents for 4DCT include 75–100 ml iopamidol (Isovue-300; Bracco, Princeton, NJ) or iohexol (Omnipaque 350, GE Healthcare) injected via a 20-G cannula in a right antecubital vein at a rate of 3–4 mL/s followed by a saline chaser. At our institution we use 75 ml iohexol 350 injected at a rate of 4 ml/s followed by 40 ml saline. In 2015 Lawson et al. published a video manuscript discussing the 4DCT technique employed at the University of Arkansas for Medical Sciences [12].

Anatomic coverage for multi-phase parathyroid is typically smaller than that of neck CT examinations performed for other indications, the vast majority of which require a single-acquisition phase, in order to minimize the radiation dose to the patient. Cephalad coverage typically begins at the angle of the mandible and extends through the aorticopulmonary window or carina. Some centers further constrain the area of coverage on the pre-contrast phase from the hyoid bone to the clavicular head based with the primary utility of this phase being for differentiation of orthotopic parathyroid lesions from thyroid nodules. Additional scan parameters include field of view 180 mm, 120 kV (peak), and automatic tube current modulation with maximum of between 400 and 700 mA. Many centers set a higher threshold mA for the arterial phase acquisition (700 mA) and a lower maximum threshold of 400 or 500 mA for the pre-contrast and delayed phases as a further means to reduce patient radiation exposure. Detector configuration will vary according to each institution's available hardware. At our center we use a 64×0.625 mm configuration. Contiguous axial images of each phase reconstructed at 1 mm are sent to the picture archiving and communication system (PACS) for interpretation and are available for customized multi-planar reconstructions as required for problem solving (Fig. 14.4). Axial, sagittal, and coronal 20 mm thick reconstructions of each phase are also made available on PACS.

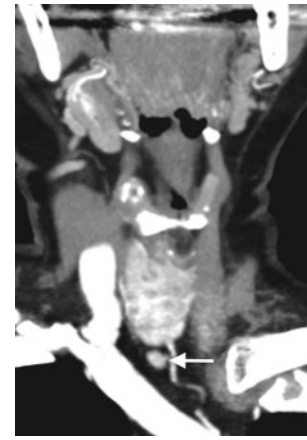

Fig. 14.4 Oblique maximum-intensity projection (MIP) image reconstruction allows image data from several slices to be combined in order to display the spatial relationship of a candidate lesion, in this case a right inferior quadrant adenoma, to adjacent vasculature for purposes of surgical planning

Test Characteristics

High variability of the reported sensitivity of US and MIBI has led to questions regarding the reliability of these exams as primary directors of surgical site and approach for MIP. In patients with primary hyperparathyroidism, sensitivity of US has ranged from 69 to 92 % and from 50 to 85 % for MIBI (Berber 2008). Operator dependence is likely a major contributing factor toward variability of the success of US. The basis of the variable success with which MIBI is able to correctly localize parathyroid lesions is less clear. Both of these modalities are thoroughly discussed elsewhere within this text.

In their initial manuscript describing the 4DCT technique, Rodgers et al. achieved a sensitivity of 88 % for lateralization and 70 % for correct quadrant localization of single-gland disease [2]. Since that time other groups, likely with the benefit of experience and optimized techniques, have built upon this earlier work and produced sensitivities for precise quadrant localization up

Table 14.1 Test characteristic of 4DCT across the literature

Study author	*Subjects*	*4DCT sensitivity Single-gland disease Lateralization*	*4DCT sensitivity Single + multi-gland disease Lateralization*	*4DCT sensitivity Single-gland disease Quadrant localization*	*4DCT sensitivity Single-gland + multi-gland disease Quadrant localization*	*4DCT sensitivity Multi-gland disease localization*
Rodgers et al. [2]	75	88 %		70 %		
Harari et al. [13]	63		85 %		66 %	
Zald et al. [14]	223		89 %		77 %	
Beland et al. [15]	25			82 %		
Starker et al. [16]	87		94 %		86 %	
Chazen et al. [17]	35	92 %		86 %		43 %
Kukar et al. [4]	200			88 %		32 %
Raghavan et al. [5]	29		92 %		82 %	
Hoang et al. [11]	94			94 %		59 %

to 94 % [7]. Reported sensitivities from various publications dating from 2006 to 2015 can be found in Table 14.1. As a caveat to interpreting this table, varying calculation methodologies and differing proportions of multi-gland disease across studies must be taken into consideration when comparing results from one study to another. While some groups report sensitivity across an entire cohort, others have chosen to separate subjects into those with single-glandular disease and performed a separate analysis for subjects with multiple adenomas or multi-gland hyperplasia. Across studies, the sensitivity of 4DCT for multi-gland disease is less than that for single-gland disease. That said, sensitivities from 32 to 59 % in multi-gland disease exceed those reported for other localization modalities (Fig. 14.5).

Beyond improved sensitivity of 4DCT compared to other localization modalities, the superior spatial resolution of CT relative to nuclear scintigraphy is immediately applicable to the goals of the minimally invasive parathyroid surgeon (Fig. 14.6). In a study of sestamibi-negative patients, average operative time was decreased from 73 to 55 min in patients receiving preoperative 4DCT [13]. Further, length of hospital stay has been shown to be shorter for those patients undergoing parathyroidectomy for whom 4DCT was obtained relative to patients who did not receive preoperative CT [18]. The effect of 4DCT on total cost of treatment for patients with primary hyperparathyroidism has yet to be conclusively determined.

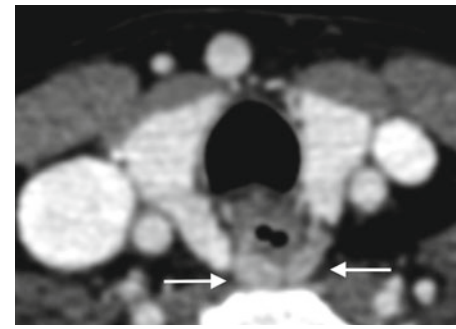

Fig. 14.5 An axial delayed-phase image at the level of the thyroid gland demonstrates paired retroesophageal parathyroid adenomas that display lower attenuation than the adjacent thyroid gland due to washout

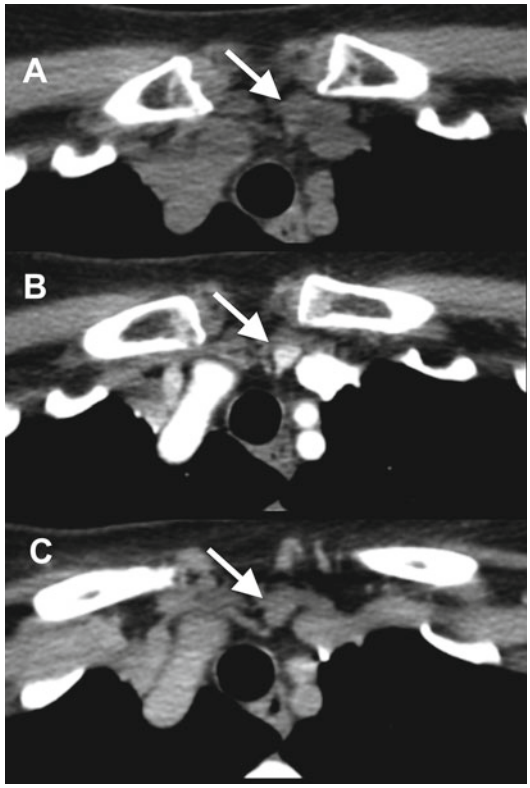

Fig. 14.6 Axial 4DCT images from the pre-contrast phase (**a**), arterial phase (**b**), and delayed phase (**c**) show a 9 mm adenoma posterior to the sternal notch and within 1–2 mm of the left brachiocephalic vein. Demonstration of such spatial relationships is a significant advantage over nuclear scintigraphy for surgical planning

Pitfalls

Several potential pitfalls and limitations must be taken into consideration when interpreting 4DCT examinations. Artifactual obscuration of the thyroid bed and other sites of potential ectopic parathyroid lesions can be encountered as a result of streak artifact related to dense contrast with the brachiocephalic, subclavian, and/or internal jugular veins. A saline chaser following contrast injection is designed to minimize such artifact but is not entirely successful in all cases (Fig. 14.7). Metallic surgical clips in and about the thyroid bed, particularly in patients with a prior history of thyroid surgery, parathyroidectomy, or cervical spine fixation, serve as another commonly

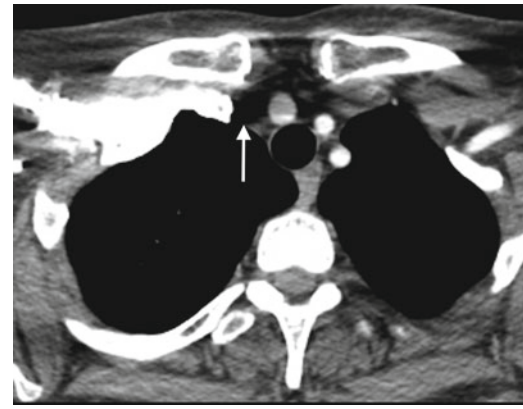

Fig. 14.7 An axial arterial phase image provides an example of artifact secondary to dense intravenous contrast, in this case contrast in the right subclavian vein leading to streaky low density obscuring the retrosternal soft tissues

encountered source of artifact in the expected region of the parathyroid glands. Physiologic attenuation of the X-ray beam related to the clavicles or shoulders (particularly in large patients) can lead to degraded image quality through the region of principal interest. For this reason, our CT technologists ask patients to lower their shoulders as much as possible during image acquisition. Patients are also asked to remain motionless throughout acquisition of each phase as motion is another common contributor to suboptimal image quality.

Reliance on predetermined time points at which to obtain arterial and delayed imaging, the standard practice at most institutions, can be problematic in patients with cardiac failure due to variations in the time at which contrast circulates from the site of venous infusion site through the arterial system. For such patients a contrast bolus tracking technique, for which scan acquisition is triggered by the appearance of contrast opacification at a certain threshold within the arterial system, provides a more reliable means with which to obtain an arterial phase scan. Other technical factors that can impact image quality include extra-venous infiltration of contrast at the injection site leading to non-opacification of the vasculature and nondiagnostic post-contrast images.

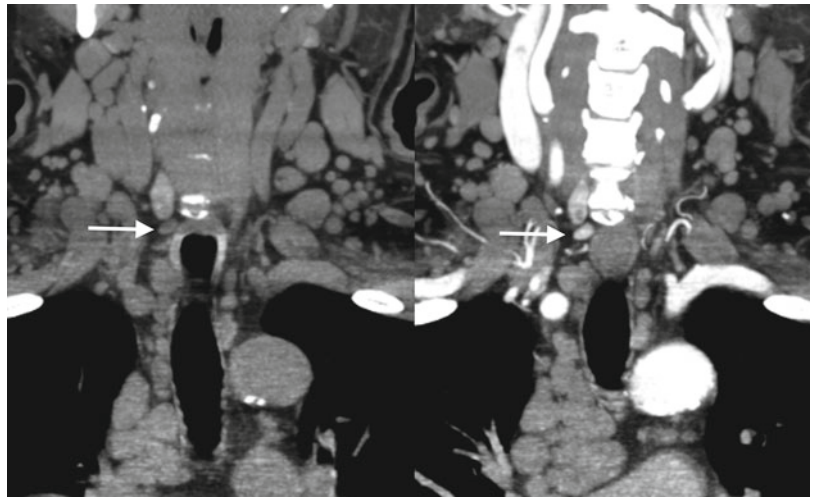

Fig. 14.8 Coronal pre-contrast and arterial phase 4DCT images in a patient with extensive cervical and mediastinal lymphadenopathy related to leukemia allow confident localization of a parathyroid adenoma in the right inferior quadrant (*arrow*). Note that on the pre-contrast phase the adenoma is indistinguishable from nearby lymph nodes

Summary

Although less than a decade has elapsed since the original published description of the technique [2], 4DCT has become an important tool for preoperative localization of parathyroid lesions in patients with primary hyperparathyroidism (Fig. 14.8). The volume of scientific literature on the topic has grown rapidly, with >50 % of papers on 4DCT appearing since 2013. Ongoing research is expected to solidify the sensitivity and positive predictive value relative to other imaging modalities, address concerns such as radiation exposure, and better define the patient population for which 4DCT is most applicable.

Society Guidelines: N/A

Best Practices

Variability of utilization of 4DCT across institutions and the relative youth of the technique (initially reported in 2006) prevent a concise statement on best practices.

Expert Opinion

CT imaging for parathyroid disease is a relatively young but nonetheless promising technique. Based on the superior sensitivity of 4DCT relative to that of ultrasound and scintigraphy for precise localization of parathyroid lesions, CT should be considered not only as a second-line tool for non-localizing patients but also as a first-line modality for preoperative localization of parathyroid disease in patients with primary hyperparathyroidism.

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Advanced Imaging of the Parathyroids

15

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Contents

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Introduction

Many surgeons advocate for two concurrent imaging studies for the purpose of localizing a parathyroid adenoma. There is level II evidence for utilizing ultrasound as first-line preoperative imaging and Tc-99 m-sestamibi (MIBI) as a confirmatory technique. When there is concordance of the findings of these two imaging modalities, minimally invasive surgery has a cure rate similar to extensive bilateral neck exploration [1, 2]. This chapter addresses the advanced imaging modalities of magnetic resonance imaging (MRI) and positron emission tomography (PET) which are not considered first-line but may prove useful in select patients. 4D computed tomography (4DCT) is a newer imaging technique which is also considered an advanced imaging modality for parathyroid adenoma localization. This is covered in a separate chapter of this book.

Magnetic Resonance Imaging (MRI)

MRI is a cross-sectional imaging modality that is not considered first-line for localizing a parathyroid adenoma. However, it may be utilized in cases when other imaging modalities have failed to localize a parathyroid adenoma, for suspected ectopic parathyroid adenoma after failed parathyroidectomy, for recurrent hyperparathyroidism

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and when patient intolerance to intravenous contrast precludes CT evaluation [2]. Overall, the sensitivity of MRI for detection of a parathyroid adenoma is reportedly between 64 and 88 % and specificity between 88 and 95 % without significant improvement over other imaging modalities [3].

Advantages and Disadvantages

Advantages include excellent soft tissue differentiation, absence of ionizing radiation, and typically a larger field-of-view which includes the head, neck, and chest. In addition, MRI sensitivity for detecting ectopic parathyroid glands in the neck and chest is reported up to 88 %. Disadvantages of using MRI for parathyroid adenoma localization include high expense and high level of patient demand (no claustrophobia and ability to follow directions) and numerous sources of false positive findings (discussed below) [4–8].

Protocol

An anterior surface neck coil should be utilized (and chest coil if the mediastinum is imaged). Images are typically acquired from the hyoid bone to the sternal notch. However, if an ectopic gland is suspected, imaging should extend below the sternal notch, and ECG-gated axial images of the mediastinum may be included. The most commonly utilized sequences are axial T1- and T2-weighted fast spin echo. Although not always necessary, fat-suppressed gadolinium-enhanced T1-weighted images may also be acquired. Some imaging centers also utilize short tau wave inversion recovery (STIR) images to improve detection of parathyroid adenomas [5]. The neck and upper chest can be examined in the transverse, sagittal, and coronal planes, also.

Typical Findings on the Various MRI Sequences

There is variability of the appearance of parathyroid adenomas on MRI. However, most commonly, they are ovoid or round structures which are hypointense on T1-weighted imaging (similar to background muscle intensity), hyperintense on T2-weighted imaging, and avidly enhance with contrast administration. When acquired, additional STIR images help highlight or enhance bright intensity parathyroid adenomas, making them more detectable on the background of fat suppression (Figs. 15.1 and 15.2). The sensitivity of STIR for parathyroid adenoma detection is reported to be around 71 % with a specificity of 94 % [5, 9]. Subacute hemorrhage in the gland can produce high signal on T1- and T2-weighted imaging. Fibrosis or old hemorrhage can cause low signal on T1- or T2-weighted imaging.

Causes of False Positive and False Negative Findings

There are a number of causes of false positive findings on MRI which include lymph nodes, thyroid nodules (adenomas, exophytic colloid cysts), enlarged cervical ganglia, and other neck masses such as sarcoid nodules and neurofibromasi (Fig. 15.3). In addition, a parathyroid adenoma may be discriminated from hyperplasia or parathyroid carcinoma based upon signal characteristics on T1- and T2-weighted imaging.

Potential causes of false negative findings on MRI include concomitant thyroid disease, the presence of parathyroid gland hyperplasia, small parathyroid gland size (glands smaller than 5 mm in size may not be seen due to limited spatial resolution), or post-surgical anatomic distortion or atypical signal. Motion and other types of artifact may also cause false negative findings [3].

Positron Emission Tomography-Computed Tomography (PET-CT)

PET-CT is now a well-recognized and well-established imaging modality which provides functional imaging integrated with the anatomic imaging component of CT. The primary radiotracer utilized (and with reimbursement) is F-18-fluorodeoxyglucose (FDG) for the purposes of oncology, cardiac viability, and neurology cases. PET-CT is not widely used nor considered

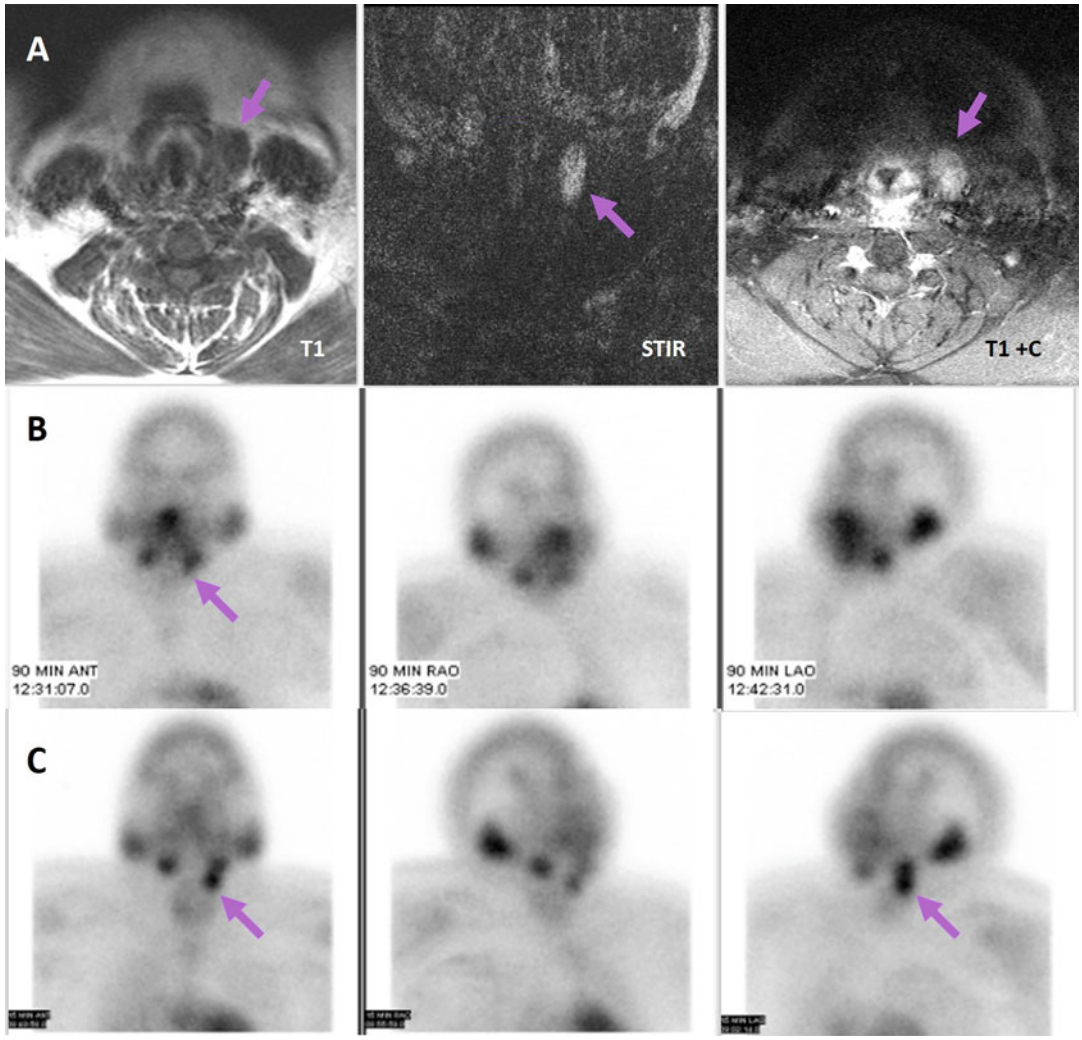

Fig. 15.1 Left superior parathyroid adenoma. A-25 year-old African-American female presented with renal disease and prior removal of three parathyroid glands due to hyperparathyroidism. Her post-surgical serum calcium and PTH were persistently elevated. Parathyroid scintigraphy with Tc-99 m-MIBI was unsuccessful for parathyroid adenoma localization (Row (**b**)). The patient then underwent MRI (Row (**a**)—T1-weighted, STIR, T1-weighted with contrast left to right) which demonstrated a left superior parathyroid adenoma. This adenoma was also demonstrated on repeat scintigraphy (Row (**c**)) performed just 3 days prior to surgery. On reexamination, it is felt that this left parathyroid adenoma was in fact present on the first set of scintigraphic images (Row (**b**); note *arrow*) but was not well-seen due to poor patient positioning on that exam. This 2 × 3 cm parathyroid gland weighed 5 g, and the intraoperative PTH (iPTH) dropped from 4090 to 463 pg/mL

a first-line imaging modality for preoperative localization of a parathyroid adenoma or even for general evaluation of the parathyroid glands. There is limited data on the use of PET radiotracers for preoperative localization of parathyroid adenomas. We briefly discuss two of these radiotracers, FDG and C-11-methionine (MET). Like MRI, PET imaging with these radiotracers may have potential utility in cases where there has been failure to localize a parathyroid adenoma with other imaging modalities, for evaluation of possible ectopic glands, or when the patient cannot receive intravenous contrast [10, 11]. One of the larger studies evaluating MET-PET for

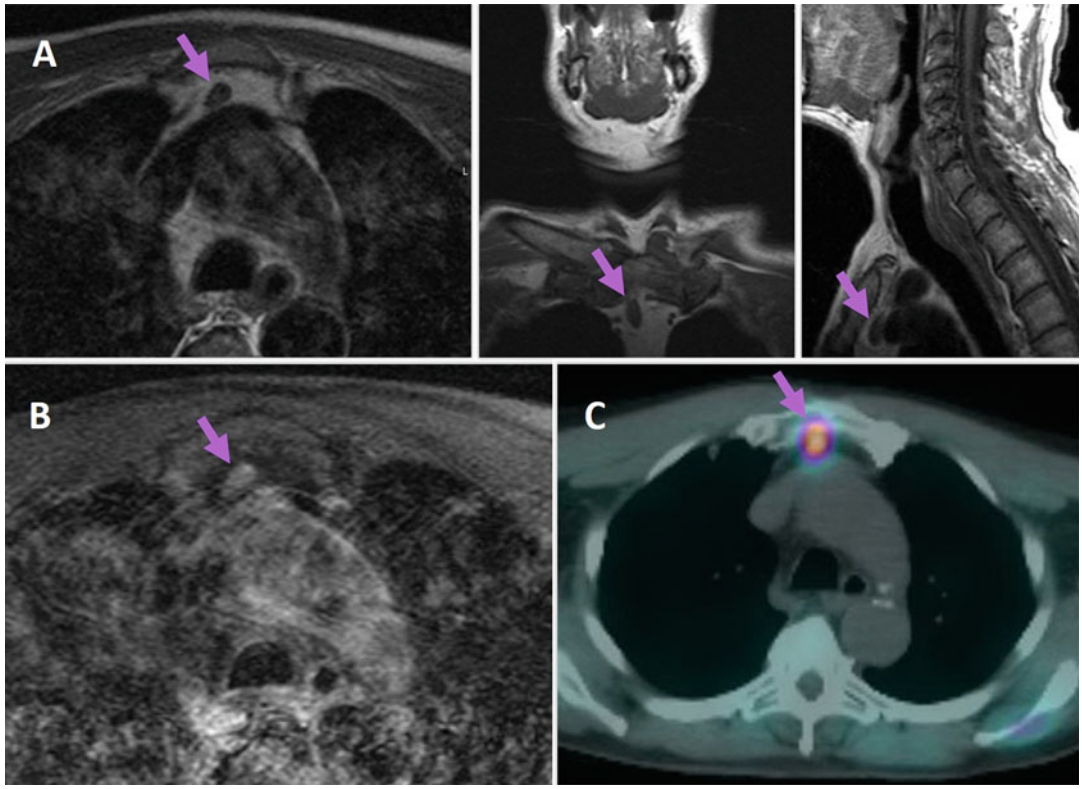

Fig. 15.2 Ectopic parathyroid adenoma. This is a 55-year-old male with an incidental finding of elevated serum calcium and PTH and diagnosed with primary hyperparathyroidism. Ultrasound demonstrated a probable 3 mm × 3 mm left superior posterior parathyroid adenoma. Subsequent scintigraphy did not localize a parathyroid adenoma. MRI was then performed ((**a**)–T1-weighted axial, coronal, and sagittal images; (**b**)–T1-weighted post-gadolinium axial view) and successfully localized an ectopic anterior mediastinal parathyroid adenoma. Scintigraphy was performed again on the day of surgery with a larger field of view and demonstrated the ectopic gland (axial SPECT/CT image shown in (**c**)). The patient then underwent mediastinal parathyroidectomy (adenoma size was 13 mm × 19 mm). iPTH dropped from approximately 170–59 pg/mL

preoperative parathyroid adenoma localization demonstrated high accuracy, a sensitivity of 91 %, and a positive predictive value of 93 %, similar to Tc-99 m-MIBI single photon emission tomography [12]. A meta-analysis by Caldarella et al. also demonstrated MET-PET to be a sensitive and reliable tool for patients with suspected parathyroid adenoma [13]. Regarding FDG, Neumann et al. found that FDG-PET had higher sensitivity for detecting a parathyroid adenoma compared to Tc-99 m-MIBI SPECT, which they felt might have been related to the size of the gland and the better spatial resolution of PET [14].

FDG is produced by a cyclotron and has a positron mode of decay with a half-life of approximately 110 min. Uptake is based upon glucose metabolism (FDG being a radiolabeled "sugar") with increased accumulation in areas of tumor, inflammation, and infection. Such is the basis of preferentially increased FDG uptake in an abnormal parathyroid gland or adenoma [14].

MET is also produced by a cyclotron and has a positron mode of decay, though it has a half-life of only 20 min. Methionine is a naturally occurring amino acid, and its accumulation (predominately through an active transport mechanism) in the body occurs in cells with a high demand for this amino acid [14–16]. Thus, greater accumulation is seen with benign or malignant tumors (i.e., parathyroid adenomas) as well as with inflammation.

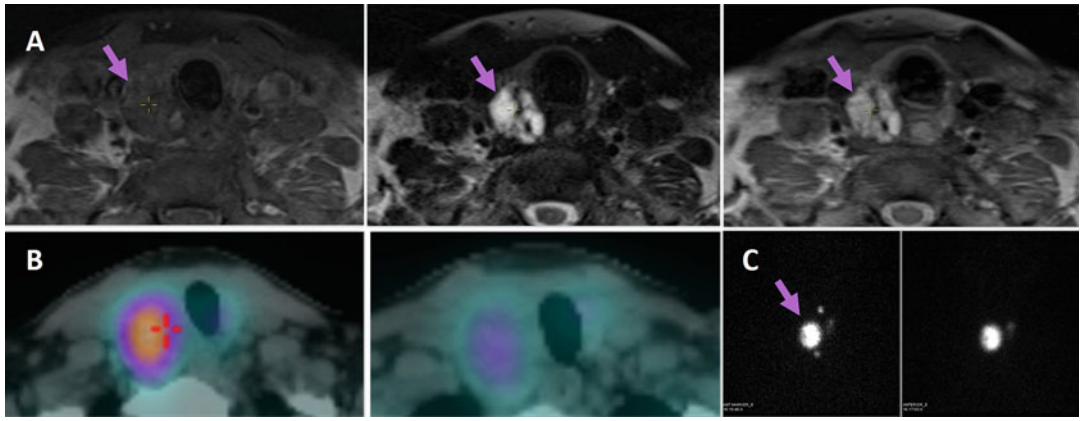

Fig. 15.3 Thyroid adenoma. This is a 35-year-old euthyroid female who was diagnosed with primary hyperparathyroidism. An outside ultrasound showed a thyroid nodule in the right thyroid lobe, but an outside sestamibi scan reportedly did not localize a parathyroid adenoma. The patient then underwent MRI which demonstrated a relatively isointense mass on the right on T1-weighted imaging (Row (**a**), left image) which was hyper-intense on STIR (Row (**a**), middle image) and enhanced (Row (**a**), right image—post-contrast T1-weighted image). The patient then underwent a second confirmatory sestamibi scan at our institution, which did not demonstrate typical findings of a parathyroid adenoma, but was suspicious for a thyroid adenoma. Therefore, the patient underwent an I-123 scan which demonstrated a hot right thyroid lobe nodule with 4- and 24-h uptake values of 18 % and 41 % respectively. It was then felt that this represented a toxic thyroid adenoma. At surgery, a dominant hyperplastic right thyroid nodule and bilateral superior parathyroid adenomas were found (there was >50 % post-excision drop in iPTH for both of these parathyroid adenomas during surgery.). Of note, the parathyroid adenomas were not detected on scintigraphy, and the finding on MRI was false positive for parathyroid adenoma

Advantages and Disadvantages

As mentioned, one advantage of PET-CT imaging for the detection of parathyroid adenomas is its higher spatial resolution, and thus, the potential for detection of smaller adenomas, as compared to Tc-99 m MIBI scintigraphy. PET-CT is also a whole-body imaging approach, and this may offer even greater advantage for detection of an ectopic parathyroid adenoma in the neck or chest. As with the use of an intraoperative gamma probe after Tc-99 m-MIBI administration, there is also interest and on-going development of hand-held beta-probe devices for PET to assist in localizing and confirming the of excision of F-18-FDG-avid tumors [17, 18]. In the future, this tool may become increasingly beneficial when utilizing PET radiotracers.

One disadvantage of PET-CT as compared to other imaging modalities is its higher cost (although, a cost-benefit analysis needs to be performed for this technique for the purpose of parathyroid localization) [19]. In addition, false positive findings may occur with inflammation. Another disadvantage regarding C-11-MET specifically is that this radiotracer is not currently reimbursed, and there is lack of commercial availability.

Protocol

A typical activity for either FDG or MET would be 10–20 mCi (370–740 MBq) administered intravenously. Standard PET/CT imaging typically occurs at 10–40 min post-injection of C-11-MET and usually around 60 min for FDG with images extending from the skull vertex to at least the lower mediastinum. A dedicated high resolution head and neck PET/CT protocol would optimize findings but is optional.

There should a minimum of 4–6 h of fasting prior to the radiotracer injection. In addition, strenuous exercise or long-acting insulin injections after midnight on the evening prior to FDG administration should be avoided.

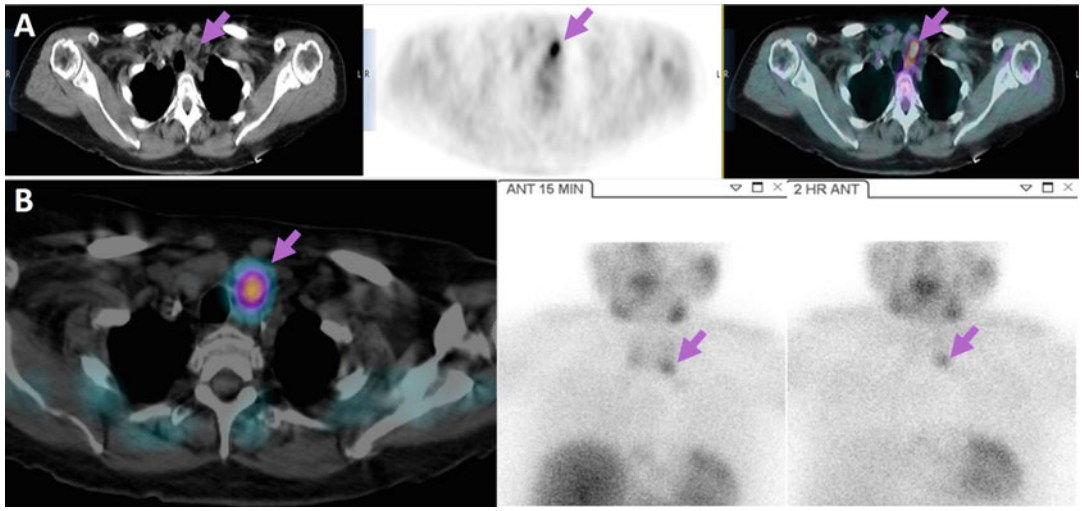

Fig. 15.4 Left inferior parathyroid adenoma. This is a 74-year-old female who underwent FDG PET-CT imaging for an unrelated oncologic abnormality, and in whom focal uptake was seen in a soft tissue lesion located at the postero-inferior aspect of the left thyroid lobe (Row (**a**)). The patient was found to have elevated serum calcium and PTH levels. A subsequent ultrasound demonstrated this to be a parathyroid adenoma which was confirmed also on Tc-99 m-MIBI planar and SPECT/CT imaging (Row (**b**)). The excised gland weighed 1.45 g and measured 2.1 × 1.3 cm. iPTH dropped from 778 to 72 pg/mL

Typical Findings on PET-CT

As with any FDG study, the focus on PET is any abnormally increased accumulation of the radiotracer ("hot spot") (Fig. 15.4). This is also the case when utilizing C-11-MET. The CT portion of the PET offers the advantages of anatomic localization, lesion size, or volume measurements (depending upon the interpretation software utilized), and attenuation correction of the PET.

Currently, there is limited data on semiquantitative lesion measurements with the calculation of standardized uptake values (SUV) for PET imaging of the parathyroid glands. Sundin et al. reported an increase in parathyroid adenoma SUV's with increasing intact serum PTH and calcium values as well as a correlation between SUV and lesion weight when utilizing C-11-MET [20]. SUV (parathyroid)/SUV (cervical soft tissue) and SUV (parathyroid)/SUV (thyroid tissue) target-to-background and target-to-non-target ratios, respectively, have also been described with C-11-MET imaging. The highest ratios were obtained at 10 and 40 min post-injection of the radiotracer, and the authors suggested imaging at these two time points to achieve optimal visualization of the parathyroid glands [21].

Causes of False Positive and False Negative Findings

As already mentioned, uptake of these radiotracers can not only be seen in benign or malignant tumors, but also with inflammation and infection—confounding the picture and giving false positive findings (Fig. 15.5).

Some potential causes of false negative findings on PET include small and lightweight parathyroid adenomas (mean size of 1.09±0.41 cm and mean weight of 0.37±0.29 g in one study) [12].

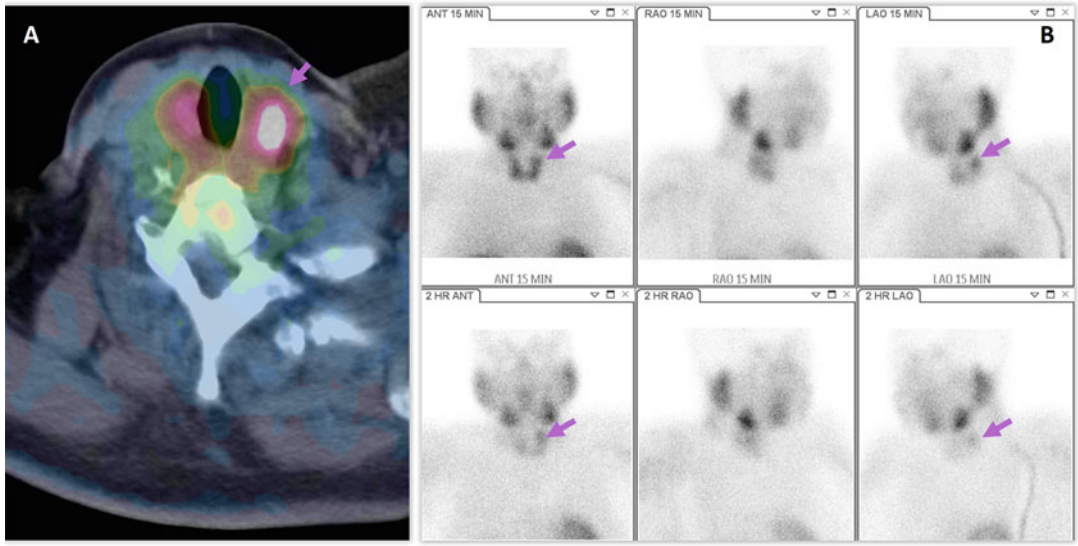

Fig. 15.5 Left superior parathyroid adenoma and thyroiditis. This is a 63-year-old female with primary hyperparathyroidism. She underwent FDG-PET/CT for restaging of multiple myeloma after chemotherapy. Diffuse nonspecific uptake was noted in the thyroid gland as well as more focal uptake in the region of the superior left thyroid lobe (Image (**a**)—selected axial FDG-PET/CT image). Follow-up Tc-99 m-MIBI scintigraphy (image set (**b**)) demonstrated a probable left superior parathyroid adenoma. A parathyroid adenoma was excised in this region, and the iPTH dropped from 133 to 32 pg/mL. A subsequent PET-CT demonstrated resolution of the prior inflammatory thyroid uptake

Summary

Based upon current literature and evidence, the first-line imaging modalities for localization of a parathyroid adenoma prior to surgery are neck ultrasound and Tc-99 m-MIBI scintigraphy. 4D CT is an up and coming modality which may supplant Tc-99-MIBI imaging in the future. When further evaluation is warranted, such as for an ectopic gland or non-localization of a parathyroid adenoma with ultrasound or Tc-99 m-MIBI, advanced imaging such as MRI, PET, and 4DCT (discussed in a separate chapter) are available. MRI offers excellent soft tissue discrimination. PET offers high sensitivity and the potential for intraoperative probe analysis.

Society Guidelines

1. Greenspan BS et al. SNM practice guideline for parathyroid scintigraphy 4.0. J Nuc Med Technol. 2012; 40:1–8.
2. ACR-ASNR-SPR practice parameter for performance of Magnetic Resonance Imaging (MRI) of the Head and Neck. 2014.

Best Practices: N/A

Expert Opinion
Advanced imaging (MR or PET) should be held in reserve when traditional imaging modalities fail to localize an offending parathyroid(s). These modalities may be useful, where available, in revision parathyroidectomy cases.

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Selective Angiography

16

Neveen A.T. Hamdy

Contents

Introduction

In primary hyperparathyroidism, the source of increased parathyroid hormone secretion is a single adenoma in more than 80–85 % of cases, multiple-gland disease due to four-gland hyperplasia or a double adenoma in 10–15 % of cases, and parathyroid carcinoma in <1 % of cases. The treatment of choice is surgery, which is the only definitive therapy, leading to durable cure. Up till two decades ago the standard surgical approach for parathyroidectomy was a bilateral neck exploration, with visualization of all four parathyroid glands, and resection of the pathological one(s), an approach which is still favored in suspected multiple-gland hyperplasia. In the hands of experienced surgeons, conventional bilateral neck exploration results in complete cure in more than 95 % of cases, with a low complication rate of 0–2.7 %.

In recent years, minimal invasive surgery has gained increasing popularity in the management of primary hyperparathyroidism, with cure rates reported to be equal if not superior to those of bilateral neck exploration, again in the hands of experienced surgeons. The success of the minimal invasive approach is conditional, however, on the mandatory accurate preoperative localization of the pathologic parathyroid gland(s). Over the last two decades, this prerequisite has led to the development of increasingly sensitive nonin-

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vasive imaging techniques, the primary localizing value of which has been largely established in the unexplored patient, with a reported sensitivity of up to 90 % for Tc99m MIBI-SPECT and ultrasound of the neck prior to initial surgery. The additional development of intraoperative quick PTH measurements further secured the chance of cure while minimizing complications by decreasing operating time.

Despite the exceptionally high cure rate observed with both surgical approaches used in the management of hyperparathyroidism, this may persist or recur in 2–7 % of cases. The most commonly reported causes for this are missed multiglandular disease, supernumerary or ectopic located glands, local recurrence or metastases from parathyroid carcinoma, or parathyromatosis due the inadvertent seeding of pathological parathyroid cells at initial or subsequent surgeries. Failure of initial surgery may also be due to suboptimal accuracy of the preoperative localizing imaging techniques used before minimally invasive surgery.

In persistent or recurrent hyperparathyroidism, re-operation represents a greater challenge than initial surgery, also for the experienced surgeon. This is largely because of the inherent risk of complications attached to the increased complexity of operating in a field in which distortion and scarring of surgical planes caused by previous surgical interventions are frequently encountered. The risk of injury to the recurrent laryngeal nerve has thus been shown to be clearly increased, so has the risk of permanent hypoparathyroidism. There is clear evidence that the success of remedial surgery for hyperparathyroidism largely depends on the accurate anatomical localization of the elusive pathological parathyroid gland(s) prior to surgical intervention. This ensures the highest probability of cure, and a favorable complication profile by reducing the risk of lengthy explorations. Most localizing noninvasive imaging techniques have been found, however, to be wanting in the localization of the source of hypersecreting parathyroid tissue in a not insignificant number of patients with challenging persistent or recurrent hyperparathyroidism, particularly those who had undergone multiple unsuccessful surgical interventions. Failure of noninvasive imaging was found to be mostly due to small size of the residual pathological glands, the higher likelihood of hyperplasia, and the inevitable disturbance of the vascular supply of the parathyroids as a result of the initial or subsequent surgical procedures.

Selective Venous Sampling for PTH

In contrast to the noninvasive imaging techniques used in the localization of pathological parathyroid glands such as Tc^{99m} sestamibi scan, ultrasound of the neck, CT scan, MRI scan, or more recently 18-FDG, ^{11}C-methionine, or ^{11}C-choline PET scans, which rely on the accurate "anatomical imaging" of one or more pathological parathyroid glands, selective venous sampling (SVS) for PTH relies on the provision of "biologic imaging" of a hypersecreting pathologic parathyroid gland. Success of this imaging modality requires knowledge of the embryology, anatomy, and venous drainage of the parathyroid glands. Normal parathyroid glands drain through the superior, middle, and inferior right and left thyroidal veins, but drainage pattern is variable, particularly in the case of ectopic parathyroid glands, or when venous anatomy is disturbed by previous surgery [1].

The principle of the technique of SVS for PTH is the collection of small amounts of venous blood from multiple closely sited locations in the neck and mediastinal veins to identify the anatomical location of veins with an abnormally high concentration of parathyroid hormone (PTH), indicating the area of drainage of a hypersecreting parathyroid gland. Venous drainage of the parathyroids, whether altered surgically or due to an anatomic variation, will eventually drain in one of several predesigned venous sampling locations.

Technique of Selective Venous Sampling for PTH

Selective venous sampling for PTH was only made possible after the first-generation radioimmunoassays (RIA) for PTH, developed in the early 1960s, were made available for use in the

clinic [2]. These assays were superseded in the late 1980s by the more reliable second-generation PTH assays measuring full-length 1–84 PTH using immunoradiometric assays [3, 4].

Selective venous sampling (SVS) for PTH is an out-patient procedure, conducted under fluoroscopic guidance in the angiography suite of a radiology department by an experienced intervention radiologist. Laboratory screening before the procedure includes a coagulation screen and evaluation of renal and thyroid function to establish the safety of contrast administration.

A variably 4-French (F), 5-F, or 7-F catheter is introduced via a sheath in the right femoral vein using the Seldinger technique, after local infiltration of the area with 1 % lidocaine. The position of the catheter is guided throughout the procedure by fluoroscopy and documented by the injection of small amounts of contrast material.

A specific map of the regional veins of the neck and mediastinum is used for guidance for PTH sampling. At the start of the procedure the catheter tip is directed through the inferior vena cava, right atrium, and superior vena cava to a position as high as possible in an internal jugular vein and slowly withdrawn within the vein, collecting in the process 2–4 ml of blood at close intervals. The procedure is repeated for the contralateral internal jugular vein, the brachiocephalic and subclavian veins, superior vena cava, azygos and semi-azygos veins, right atrium and inferior vena cava, and common hepatic vein, covering the venous drainage of normal anatomic locations as well as potential ectopic locations of parathyroid glands. Two further samples are taken from the femoral vein for measuring peripheral blood PTH concentration. The samples are collected in whole-blood tubes with spray-coated EDTA and immediately placed on ice before transportation to the laboratory for PTH measurements. All sampling sites are documented using spot-film radiography. Sample number and matching anatomical location of sampling are very accurately recorded to enable comparison of PTH assay results with the location of each sample later. This represents a crucial step of the procedure to ensure a reliable outcome for SVS. Results of PTH measurements are added to the recording sheet on their return from the laboratory after analysis in one batch using an intact PTH radioimmunometric or immunochemiluminescent assay. The site of an abnormally high PTH concentration is cross-referenced to the recorded sample source and results are recorded on the anatomic sampling map.

A ***PTH gradient***, defined as a 50 % increase in plasma PTH concentration compared to peripheral measurements, provides the anatomic localization of the draining area of a hypersecreting parathyroid gland [5]. Although not providing an accurate localization for the abnormal parathyroid gland, the anatomic site of a PTH gradient enables the identification of the region of pathology (side of neck/mediastinum). The area with the highest gradient helps to protocol further confirmatory CT or MRI examinations. The combination of "biological" and "anatomical" imaging significantly increases the chances of guiding the surgeon to a more accurate anatomical localization of a pathological parathyroid gland and thus to a more secure surgical outcome (Fig. 16.1).

Value of Selective Venous Sampling for PTH in the Localization of Pathological Parathyroid Glands in Hyperparathyroidism

Selective venous sampling of neck and mediastinal veins for PTH enjoyed a period of favor as a valuable method for localizing hyperactive parathyroid glands for a decade after being first described by Reitz et al. in the New England Journal of Medicine in 1969. The first following case series reporting the use of SVS for PTH as an imaging modality in hyperparathyroidism were not only performed in persistent or recurrent hyperparathyroidism, but also as a primary localization tool, when noninvasive techniques failed to localize a pathological parathyroid gland [2, 7, 8]. Results from these early studies on the value of SVS for PTH are confounded, however, by the then use of less reliable PTH assays, by the restricted number of samples collected during the original conventional SVS procedure, and by the absence of reliable noninvasive imaging techniques till the late 1980s, when it was

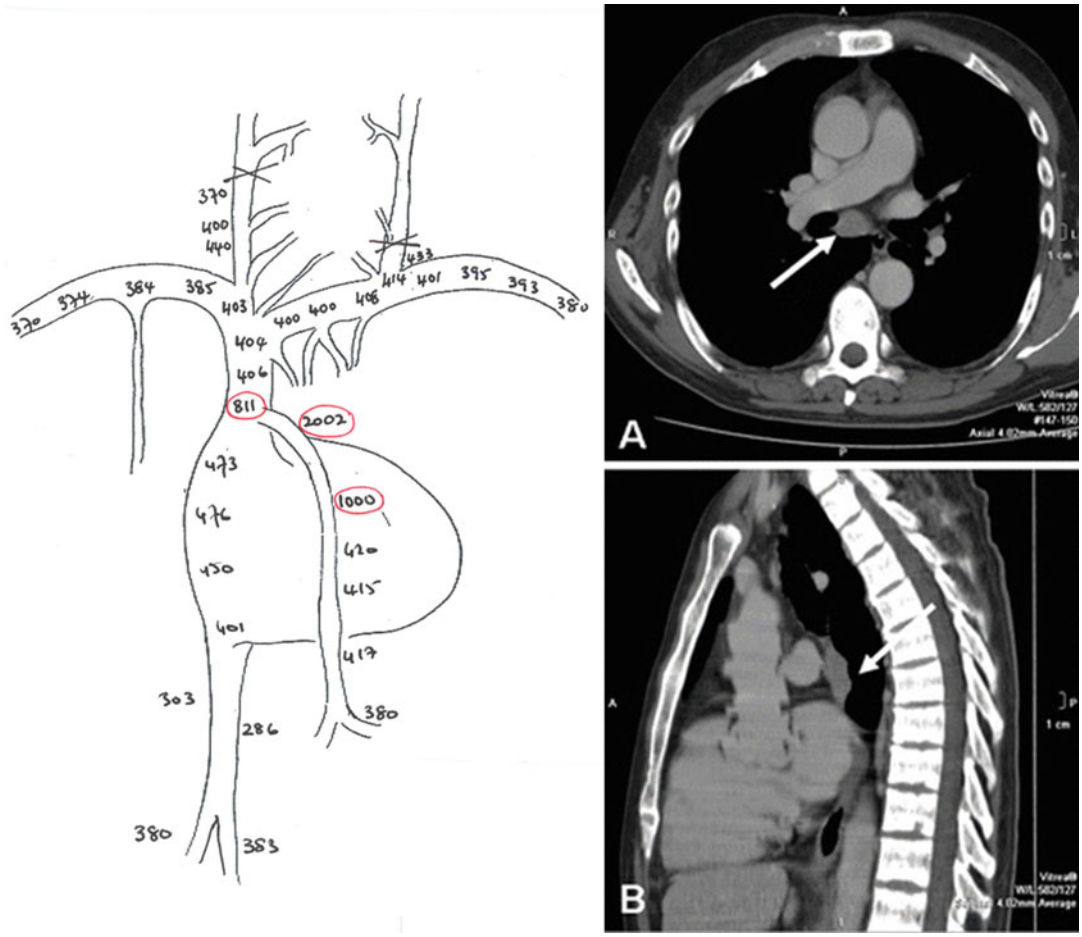

Fig. 16.1 PTH cartography of selective venous sampling (*left panel*) in a 42-year-old patient with severe recurrent parathyroid carcinoma and very high circulating intact PTH levels (380 pmol/l to normal <8 pmol/l), suggesting a mediastinal source for the very high PTH gradient in samples obtained from the origin of the azygos vein (2002 pmol/l), and from the superior vena cava at the level of thoracic vertebra 5 (811 pmol/l) and at the level of the left main bronchus (1003 pmol/l). CT scan of the thorax confirmed the localization suggested by SVS by demonstrating a large (4 ×3 ×2 cm) subcarinal mediastinal lymph node metastasis (*white arrow*), which was successfully excised resulting in a year-long complete remission (case report [6])

accidentally discovered that technetium 99m methoxyisobutylisonitrile (sestamibi), initially introduced for cardiac scintigraphy, also concentrated in parathyroid adenomas [9]. Data from these earlier studies are not further discussed in this section as they are inconsistent and less reliable than evidence obtained from more contemporary clinical series.

In 2009, Mihai et al. conducted an evidence-based analysis of data from studies published from 2002 to 2008 on the value of imaging modalities for primary hyperparathyroidism, including selective venous sampling for PTH, in the primary operation setting as well as for re-operative procedures. Sensitivity of SVS was found to be high in the unexplored patient: 94.7 % [10] and 87 % [11], as well as in the re-operative setting for persistent or recurrent hyperparathyroidism: 91 % [12], 83 % [13], 81 % [14], 78 % [15], 75 % [16], and 93 % with using the newly developed quick PTH assay during SVS [17]. As similar high sensitivities were obtained with sestamibi scintigraphy and ultrasound of the neck before initial surgery, it was judged that the use

of the invasive procedure of SVS should be reserved to cases with persistent or recurrent hyperparathyroidism, in which noninvasive imaging studies are negative or discordant. Whereas the authors of this analysis state that from an evidence-based view, none of the available studies provided a high enough level of evidence to allow confident recommendations, they go on to point out that SVS is highly recommended by several authors, particularly when guided by quick PTH measurements during the procedure [12, 17]. They do also issue recommendations grade B based on an overall level of evidence of 4, suggesting that in case of re-operation, selective venous sampling for PTH is advised when sestamibi scintigraphy, ultrasound of the neck, CT, and MRI are negative or inconclusive [18].

A systematic review of all clinical trials and review articles published since 2000 on the implications of parathyroid localization methods, including selective venous sampling, on the clinical management of hyperparathyroidism, was further undertaken in 2013 by Kunstman et al. The authors outline the important role of venous sampling in remedial cases, and go on to stress again, similar to their predecessors [18], that based on available evidence, the only indication for this invasive procedure is in patients with persistent or recurrent hyperparathyroidism or in those who have undergone extensive neck surgery, and who have equivocal, discordant, or negative noninvasive localization studies [19].

A systematic meta-analysis of the international literature, conducted in 2004, extended the analysis of the predictive value of selective venous sampling for PTH to patients with persistent or recurrent renal hyperparathyroidism. In this analysis, the localizing value of SVS was compared to that of noninvasive imaging techniques when these were positive as well as when they were negative in localizing a pathological parathyroid gland. Based on their findings, the authors conclude that in persistent or recurrent renal hyperparathyroidism, SVS performed by an experienced investigator acquiring 20–30 samples per investigation shows excellent results in case of inconclusive noninvasive localization studies [20].

A retrospective analysis of a prospective database of 31 patients referred for remedial surgery who had undergone real-time quick PTH superselective venous sampling (sSVS) in the setting of negative noninvasive imaging modalities demonstrated that superselective SVS correctly predicted the localization of the affected gland in 89 % of cases. These data further consolidate the view that real-time sSVS is a valuable tool in guiding remedial parathyroid surgery [21].

Selective venous sampling for PTH was also shown to improve the sensitivity and accuracy of four-dimensional computed tomography (4D-CT) in the localization of a parathyroid adenoma in a highly selective group of patients with challenging recurrent or persistent primary hyperparathyroidism and negative 99mTc-MIBI and ultrasound scans. Whereas using 4D-CT alone yielded a sensitivity of 50 %, combining it with SVS increased the detection sensitivity for the elusive pathological parathyroid gland to 95 % [22].

Factors Affecting the Sensitivity of SVS for PTH

Our group undertook an analysis of factors affecting the sensitivity of 20 SVS for PTH in a case series of 18 patients with persistent or recurrent hyperparathyroidism, more than half of whom had two or more previously failed surgical interventions. All had also noninvasive diagnostic imaging using Tc-99m-MIBI-SPECT [6]. SVS for PTH, during which a minimum of 30 samples were collected from neck and mediastinal veins, was able to pre-operatively accurately localize 15 of 20 pathological parathyroid glands, which were subsequently removed at 20 revision surgeries (sensitivity 75 %), compared to a sensitivity of only 30 % for Tc99m-MIBI-SPECT. Ten of the 15 glands removed at re-operation (7 hyperplastic glands and 3 adenomas) were found in normal anatomical locations, and 5 glands in ectopic locations: 4 in the mediastinum and 1 high in the left side of the neck on the prevertebral fascia [23].

The sensitivity of SVS was found to be affected by ***anatomically expected versus ecto-***

pic locations of the pathological glands. SVS was thus able to accurately localize 10 of 14 pathological glands found in normal anatomical locations (71 %) and 5 of 6 pathological glands found in ectopic locations (83 %): mediastinum $n=4$ and high in the neck on the prevertebral fascia $n=1$.

The sensitivity of SVS was also determined by the ***pathology of the abnormal parathyroid gland***: SVS was able to accurately localize all 5 adenomas (100 %), 9 of 14 hyperplastic glands (64 %), and 1 metastasis from a parathyroid carcinoma (100 %) subsequently removed at surgery.

Pathological parathyroid size was also found to influence the sensitivity of SVS: this accurately localized 8 of 9 pathological glands with a diameter greater than 1.5 cm (89 %), but only 6 of 11 pathological glands with a diameter smaller than 1.5 cm (55 %), 9 of which were hyperplastic (82 %).

Number of previous surgical interventions: The sensitivity of SVS was significantly decreased after multiple surgical interventions mainly due to the technical inability to sample small veins that had been ligated or damaged by previous surgery or because of suspected parathyromatosis.

Multiple sampling sites with a PTH gradient: A gradient documented in both the distal brachiocephalic and the left jugular vein accurately corresponded with the finding of a pathological parathyroid gland in the left side of the neck at surgery in two of the two cases (100 %) (Fig. 16.2a). A gradient in both the proximal brachiocephalic vein and the vena cava superior accurately corresponded with a pathological gland in the right lower quadrant of the neck in two of the three cases (67 %). No pathological gland could be found in a third case, despite extensive neck and mediastinal exploration suggesting possible parathyromatosis, particularly as the patient had undergone multiple previous neck explorations (Fig. 16.2b). A gradient in the vena cava superior and the azygos vein accurately corresponded with a gland in the mediastinum in two of the two cases (100 %) (Fig. 16.2c).

Details of the PTH cartography at venous sampling demonstrating the large mediastinal metastasis shown in Fig. 16.2c are shown in the left panel of Fig. 16.1. The mediastinal location of a possible metastasis was confirmed by a CT scan of the thorax, demonstrating a large

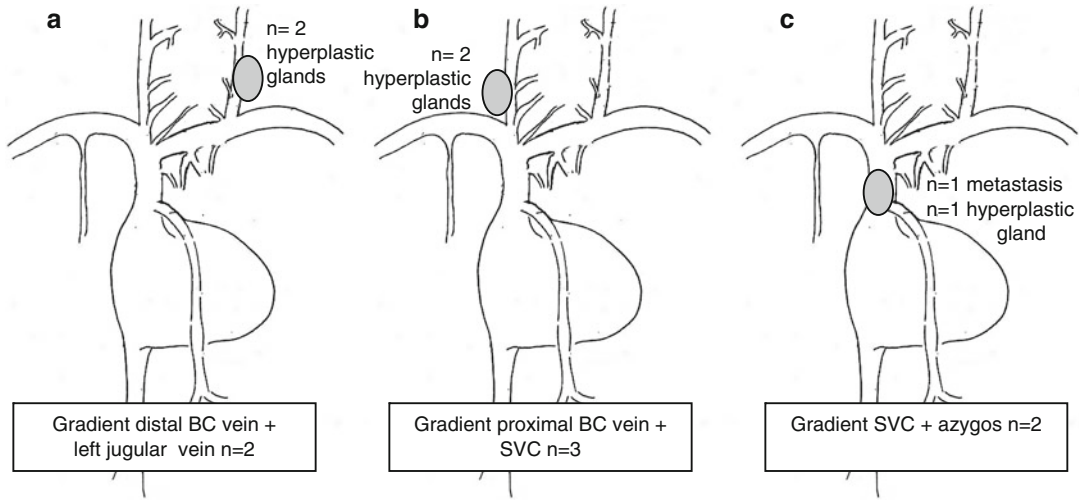

Fig. 16.2 Outcome of surgery following SVS demonstrating a gradient in the brachiocephalic (BC) vein and the left jugular vein (**a**), the brachiocephalic (BC) vein and the superior vena cava (SVC) (**b**), and the brachiocephalic vein (BC), the SVC, and the azygos vein (**c**) (case series [23])

(4 × 3 × 3 cm) subcarinal mediastinal metastasis (right panel, Fig. 16.1), which was successfully excised using a transpericardial approach. The elimination of the only source of increased PTH secretion, as suggested by selective venous sampling, was associated with a very severe and protracted hungry bone syndrome due to a year-long unmeasurable serum PTH levels, after which these started to rise again due to a new metastatic lesion localized pretracheally in the upper mediastinum [6].

Limitations and Pitfalls in the Interpretation of Selective Venous Sampling for PTH

The main indication for performing SVS for PTH is in persistent or recurrent hyperparathyroidism, when noninvasive parathyroid imaging techniques fail to provide an accurate localization for the pathological parathyroid gland. Disturbed venous anatomy and compromised vascular drainage alter the normal drainage map of the parathyroids in the region and represent the very limitation of the technique after initial and subsequent surgery. A main limitation of conventional SVS is the too low spatial resolution resulting from the too small number of samples obtained mainly from large veins (10–15 samples), and the missing out of sampling the smaller calibre ones. Single adenomas may also have more than one venous drainage, or multiple adenomas may be present. The most effective way to circumvent this limitation is the acquisition of as many samples as possible at the closest possible intervals along the sampled veins. We have shown that the collection of an average of 30–40 samples at close intervals (about every 2 cm) along the drainage areas of the parathyroid glands significantly increases the positive predictive value of the technique for localizing a pathological parathyroid gland [6]. Near-real-time quick PTH performed during the procedure allows focusing on the area demonstrating high PTH levels, resulting in a significantly increased accuracy of SVS [12, 17, 21].

There are several pitfalls in the interpretation of published SVS data. Gathered evidence has been largely based on case series, consisting mostly of small number of patients, sometimes as small as five patients. Studies have been mostly retrospective, with case series often collected over a decade or more, often not taking into account advances in imaging technology occurring over the time period. The various case series are also heterogeneous, with variable patient selection, variable histologic selection (single adenoma vs. multiple-gland hyperplasia), small (<1.5 cm) versus larger size of the pathologic parathyroid gland, and normal anatomic versus ectopic locations [6]. Variation in outcome may also be due to variation in the SVS protocol and technique over time, such as restricted number of sampling sites, planned sampling of just large veins, as well as variable but difficult-to-evaluate expertise in performing the technique, so that results may not be confidently compared between reported studies.

Last, but not least, an important pitfall in the interpretation of parathyroid diagnostic imaging modalities, whether noninvasive such as MIBI-SPECT and ultrasound of the neck, or invasive such as SVS for PTH, remains the heterogeneous and diverse definitions, such as, to name a few, accuracy, sensitivity, specificity, and positive predictive value, interchangeably used in the various reported studies to assess the value of SVS for PTH in persistent or recurrent hyperparathyroidism.

Disadvantages of SVS

The main disadvantage of SVS is that it is an invasive, time-consuming, and expensive procedure, which requires special technical expertise. The procedure may also be associated with the potential complications of all venous catheterizations, which include discomfort, bleeding, hematoma formation, venous thrombosis, pseudo-aneurysm, wound infection, and risks of using contrast material including anaphylactic reactions and deteriorating renal function. The costs of multiple PTH determinations and of the

procedure itself are also a consideration, although minimal compared to the personal, economic, and societal costs of further failed remedial surgery.

Summary

In primary hyperparathyroidism, cure rates are exceptionally high using the standard conventional bilateral neck exploration as well as the minimally invasive approach. Notwithstanding, 2–7 % of patients suffer persistent or recurrent hyperparathyroidism. Re-operation represents a significant challenge, also in the hands of experienced surgeons, and preoperative localization of the elusive pathological parathyroid gland(s) is mandatory to ensure a positive surgical outcome as well as to prevent complications attached to lengthy and extensive neck explorations. The accuracy of noninvasive imaging techniques such as Tc99m sestamibi has been well established in the primary operative setting, as well as in a number of patients with persistent or recurrent hyperparathyroidism. However, these noninvasive imaging techniques fail to guide the surgeon to the region to operate in a select group of patients with persistent hyperparathyroidism, particularly those who have undergone multiple failed surgical interventions. In this case, selective venous sampling for PTH has been shown to play an important role in the localization of elusive pathological parathyroid glands, with a sensitivity ranging from 75 to 95 % in contemporary series, with the lower reported accuracies appearing to be mainly due to limited number of samples collected during the procedure. We and others collect 30–40 samples with very positive outcome. Sensitivity is clearly enhanced by the use of near-real-time quick PTH, which allows the radiologist to obtain more selective samples from the area identified as having the highest PTH concentration. Re-operative cure rates as high as 98 % have been reported for persistent or recurrent hyperparathyroidism when intraoperative rapid PTH is additionally measured during surgery.

None of the studies addressing the value of SVS for PTH provide a high enough level of evidence (overall EBM 4), as available evidence is largely based on small case series and few but well-performed observational studies. Selective venous sampling is nevertheless highly recommended in patients with persistent or recurrent HPTH in the presence of negative or discrepant results from noninvasive localization studies, for orientation towards the anatomical location (indication of laterality in neck or localization in mediastinum), with further confirmation of the localization by focused noninvasive imaging modalities (CT scan or MRI). The evidence level and subsequent recommendations should clearly be integrated with availability of the technique, individual clinical expertise in its use, and costs of the procedure.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion

In experienced hands, selective venous sampling for PTH is a safe and invaluable adjunct to the armamentarium of noninvasive parathyroid diagnostic imaging modalities used in the re-operative setting in patients with persistent or recurrent hyperparathyroidism, when these are negative, dubious, or discordant, failing to guide the surgeon to the area to operate.

The procedure requires special technical expertise and the key to its success is the superselective approach, with the collection of at least 30 samples covering all potential areas of venous drainage of a pathological parathyroid gland. Additional near-real-time quick PTH measurements enhance the outcome of the procedure. Combining these measures with intraoperative PTH significantly increases the chance of cure and provides a favorable complication profile in the difficult-to-manage patient with persistent or recurrent hyperparathyroidism.

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Part VI

Surgical Treatment of Parathyroid Disease

Minimally Invasive Radioguided Parathyroidectomy

17

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Contents

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Primary Hyperparathyroidism

Pathophysiology

Primary hyperparathyroidism is the syndrome of hypercalcemia resulting from elevated levels of parathyroid hormone (PTH) and this is the most common cause of hypercalcemia in a non-hospitalized patient [1]. The most common cause of 1° HPT is a solitary parathyroid adenoma, characterized clinically by autonomous hyperfunction and histologically by hypercellularity within that gland. A solitary parathyroid adenoma accounts for 85–90 % of cases of 1° HPT. Less common causes include multiple (usually double) adenomas (2–4 %) or four-gland hyperplasia (4–5 %) [2].

Epidemiology

1° HPT occurs in approximately 1 in 500 females and 1 in 2000 males over 40 years of age per year. 1° HPT may present at any age, but is diagnosed most commonly in the fifth through seventh decades of life [3–6]. The incidence increases with age and may be up to 1 in 100 in the elderly [7].

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Clinical Features

Symptoms of 1° HPT have often been summarized by the mnemonic "stones, bones, groans and overtones." A majority of patients with 1° HPT present symptomatically, but some of these patients have nonspecific symptoms. Only a small proportion of patients are truly asymptomatic [8]. In cases where patients appear to be asymptomatic when 1° HPT is diagnosed, the severity of their neurocognitive symptoms may only be recognized after parathyroidectomy with correction of hyperparathyroidism. In addition to these subclinical neurocognitive symptoms, patients are frequently found to have diminished bone density, even in the absence of bone pain [9].

Minimally Invasive Parathyroid Surgery

Background Information and Advantages

The traditional surgical approach to parathyroidectomy, as described by Mandl in 1926, consisted of bilateral neck exploration with extirpation of the visually identified enlarged gland and at least one other normal-appearing gland. If an abnormal-appearing gland was not identified in the expected anatomic location, the surgical exploration continued superiorly toward the skull base and inferiorly into the superior mediastinum. Bilateral neck exploration remains the gold standard for surgical management of primary hyperparathyroidism and is the standard by which the efficacy of minimally invasive parathyroidectomy is judged.

A large review (20,255 patients with 1° HPT from 215 studies published between 1995 and 2003) [2] examined outcomes of MIRP and bilateral neck exploration, finding cure rates of 97 and 98 %, respectively.

There is no strict definition by which a procedure or variation of an existing procedure may be classified as "minimally invasive" and there exists some controversy as to what constitutes minimally invasive parathyroidectomy (MIP) [10]. A broad, generic definition of MIP would encompass any form of parathyroidectomy that enables the surgeon to use a smaller incision to explore one side of the neck and identify and remove the abnormal-appearing, adenomatous parathyroid gland.

Various adjunct techniques have been utilized with the intent of improving the success rate of minimally invasive parathyroidectomy. One of the most successful of these adjuncts involves preoperative administration of a radionuclide with a physiologic proclivity for localization to parathyroid tissue in combination with intraoperative measurement of specimen radioactivity using a gamma probe to confirm removal of the offending parathyroid gland [11–18]. This practice leads to the designation as "radioguided." The combination of minimally invasive techniques and intraoperative use of a radionuclide and gamma probe constitutes the technique of minimally invasive radioguided parathyroidectomy (MIRP).

Successful preoperative adenoma localization has been noted to decrease surgical time [6, 19]. With accurate preoperative adenoma localization before MIRP, the time from skin incision to removal of the offending parathyroid adenoma is usually 5–20 min, with the entire procedure completed in approximately 30 min in most cases [5]. In cases of failed parathyroidectomy, subsequent interventions were met with fewer complications in cases where the first surgery was performed using a minimally invasive approach [20]. Additionally, MIRP has been shown to remain a viable option in most patients who have already undergone attempted surgery for 1° HPT [21].

Surgical Indications

Historical indications for surgical management of 1° HPT are summarized in Table 17.1. More recently, the role for surgery in managing 1° HPT has expanded as our understanding of the long-term consequences of untreated 1° HPT has grown [22]. Parathyroidectomy has been shown to improve symptoms in patients with 1° HPT [4]. In addition to symptomatic improvement, these patients who undergo parathyroidectomy have improved bone mineral density [23] and are

Table 17.1 Historical indications for parathyroidectomy

Serum calcium >12.0 mg/dL
24-h Urinary calcium >400 mg/day
Episode of life-threatening hypercalcemia
Creatinine clearance decreased by ≥30 %
Nephrolithiasis
Age <50 years
Osteitis fibrosa cystica
Osteoporosis
Neuromuscular symptoms

at lower risk for cardiovascular disease and premature death [8, 9, 24, 25]. Parathyroidectomy is the only definitive treatment for 1° HPT and has been noted to be cost effective, whether patients are symptomatic or not [9, 26, 27].

Preoperative Evaluation

In addition to the usual preoperative history, physical examination, risk stratification, and appropriate medical optimization, several other factors must be taken into consideration prior to surgery. The surgeon must be certain that the patient does, in fact, have 1° HPT and not some other condition that may mimic 1° HPT, such as severe vitamin D deficiency (increased PTH with normal or low calcium) or familial hypocalciuric hypercalcemia (FHH). In one series, nearly 20 % of patients referred for parathyroidectomy were incorrectly diagnosed with 1° HPT [28].

In cases of proven biochemical 1° HPT, vitamin D deficiency, renal failure, heart failure, and morbid obesity, among others, may compromise the utility of adjunctive modalities, including preoperative localization imaging studies and intraoperative PTH measurements. Consideration of the findings obtained from any adjunct studies must be made in the context of the patient's comorbidities.

Preoperatively, the surgeon must assess for the presence of any voice or swallowing complaints and appropriately pursue evaluation of these. Any neck surgery may lead to subjective difficulty with swallowing and/or voice changes, especially early postoperative period. Due to the anatomic proximity of the parathyroid glands to the recurrent laryngeal nerves, it is prudent to examine vocal cord motion prior to surgery, using either laryngeal mirror examination or flexible fiber-optic laryngoscopy.

Options for Anesthesia

General anesthesia is the usual choice during MIRP, but monitored anesthesia care (MAC) with regional anesthesia (i.e., cervical block) are well-described alternatives that may also be used. In the hands of an experienced, high-volume MIRP surgeon, cases involving a localized, solitary adenoma may routinely be completed in less than 30 min. Patients with significant medical comorbidities who are otherwise unfit for general anesthesia may benefit from MAC with regional anesthesia [29]. Reliable and consistent provision of anesthesia by experienced providers is very important for a local/MAC technique to be successful.

MIRP in Specific Patient Populations

MIRP in Pediatric Patients

Primary hyperparathyroidism is rare in children, with an incidence of 2–5 per 100,000 [30]. As in the adult population, the underlying cause of 1° HPT in the pediatric population is most commonly a solitary parathyroid adenoma, accounting for 80 % of cases. Multi-gland hyperplasia is the cause in 16.5 %, double adenomas are identified in less than 1 %, and 2.6 % appeared to have normal gland histology [31]. Parathyroid carcinoma is exceedingly rare in children, accounting for far less than 1 % of cases of 1° HPT [32]. Severe neonatal hyperparathyroidism is a separate disease process and its features and management are beyond the scope of this section and are described in Chap. 19 [33].

Management of pediatric 1° HPT is similar to that in adults, but with consideration given to two points [34]. First, children are more likely than adults to have a parathyroid adenoma in an ectopic location. Second, up to 50 % of cases of multi-gland hyperplasia are related to one of the multiple endocrine neoplasia (MEN) syndromes

or familial non-MEN hyperparathyroidism. The increased incidence of multi-gland disease in children is nearly completely accounted for by the number of familial cases [35]. In children who do not have a personal or family history of a hereditary endocrinopathy, MIRP is considered to be a viable surgical option, though it has not specifically been studied in this group.

In patients of all ages, accurate preoperative localization is the key to avoiding bilateral neck exploration. In children, ultrasound and ^{99m}Tc-sestamibi SPECT were found to be accurate in 79 % and 86 %, respectively—similar figures as in adults [2, 31]. In those cases where ultrasound is non-localizing, studies that offer greater anatomic detail, such as ^{99m}Tc-sestamibi SPECT, SPECT-CT, or 4D CT, may be especially useful due to a higher incidence of ectopic parathyroid adenomas in children.

MIRP in Elderly Patients

Elderly patients may be less likely to be referred for surgery and more likely to decline surgery for 1° HPT due to perceived risks of surgery. Several studies have clearly demonstrated the quality-of-life benefits, cost-effectiveness, and safety of MIRP in older patients [7, 35–38], although a single (though much larger volume) study found a higher rate of complications in elderly patients [39]. The notable difference between these findings may be explained by the volume of parathyroid surgery performed by the surgeons whose patients were included in each study. Those patients who underwent surgery with a high-volume parathyroid surgeon tended to have shorter operative times and fewer complications than those who underwent surgery with a low-volume parathyroid surgeon [39].

MIRP in Pregnancy

Primary hyperparathyroidism poses a unique set of risks in pregnancy and surgery remains the definitive treatment. In this situation, the advantages of a minimally invasive procedure, including shorter operative time and potentially avoiding general anesthesia, are apparent. While some have advocated that the optimal timing for parathyroidectomy is early in the second trimester, this fact may be less important in the context of the danger of untreated hyperparathyroidism in pregnancy. The first goal remains localization of the diseased gland(s) with minimal or no radiation exposure to the fetus. Ultrasound is the most commonly recommended first-line study for parathyroid localization during pregnancy [40–42]. MRI and other techniques, such as needle aspiration with measurement of PTH levels of aspirate, have been described as alternatives in the context of a non-localizing ultrasound [42]. The use of sestamibi-based imaging and intraoperative ^{99m}Tc-sestamibi administration and gamma probe measurements are considered by many to be ill-advised during pregnancy [40, 41], while others have described alternative ^{99m}Tc-sestamibi dosing protocols for that may not portend significant risk to the developing fetus [43].

MIRP in Obese Patients

Obesity complicates nearly all aspects of minimally invasive surgery. In addition to the increased risk associated with anesthesia, obesity worsens the diagnostic capability of preoperative localization imaging studies and adds significant technical difficulty to the surgical procedure. High BMI may also prolong the half-life of PTH, thereby compromising the utility of intraoperative PTH monitoring [44]. Postoperatively, obesity impacts dosing requirements for oral calcium, placing these patients at higher risk for symptomatic hypocalcemia [45, 46].

Imaging and Localization

Details of technical considerations pertaining to the various choices for imaging the parathyroid glands are discussed elsewhere in this text and are beyond the scope of this section. Since

preoperative localization of the offending parathyroid adenoma is practically the *sine qua non* of minimally invasive radioguided parathyroidectomy, selected modalities will be briefly discussed with an emphasis placed on efficacy and shortcomings of each one. An overview of relevant imaging modalities may be found in Table 17.2.

Selection of preoperative localization studies depends largely on surgeon's choice and available technologies [47]. In the past, bilateral neck exploration for 1° HPT was routinely performed without any preoperative imaging. Successful localization of the offending lesion(s) helps the surgeon to utilize a smaller skin incision (improved cosmesis), avoid unnecessary bilateral neck exploration, decrease operative time and associated costs, and reduce the rate of complications while maintaining success rates that are similar to bilateral neck exploration [2, 6].

There is no perfect imaging study for localization of diseased parathyroid glands. Over time, new techniques have emerged as evolutions of older techniques. Dual-phase (or multi-phase) imaging studies, which rely on perfusion and washout of radionuclides or intravenous contrast, have offered some improvement in differentiation of parathyroid tissue from surrounding structures. In an effort to improve reliability of preoperative localization, it is the practice of some surgeons to routinely pursue two imaging studies that show concordance in location of the parathyroid adenoma.

Ultrasonography

Ultrasonography is the most commonly utilized imaging tool in the evaluation of the parathyroid disease. It does not involve radiation exposure, it is inexpensive compared to other pertinent modalities, and it is widely available, including in many clinics where patients are seen for 1° HPT. The efficacy of parathyroid ultrasonography is highly dependent upon the experience of the user. High-resolution ultrasound units with color Doppler capability allow the operator to identify the polar feeding vessel to the adenomatous parathyroid gland and to assess vascularity. Parathyroid adenomas tend to have peripheral vascularity and are typically hypervascular compared to most thyroid nodules [48, 49].

In cases of 1° HPT due to a solitary adenoma, sensitivity, specificity, and positive predictive value of ultrasonography have been reported as 70–96, 50–100, and 90–98 %, respectively [49]. In patients with co-existent nodular thyroid disease, the sensitivity of ultrasonography has been reported to be diminished to 64 % [49, 50]. Multigland disease is correctly imaged using ultrasonography with success rates ranging from 10 to 50 % for multiple hyperplastic glands and 10–35 % for double adenomas [2].

The efficacy of ultrasonography for preoperative parathyroid adenoma localization has notable limitations in several groups of patients [49]:

- Patients with multinodular thyroid disease
- Patients with a short and/or thick neck
- Patients with parathyroid adenoma(s) in "sonographically silent" areas, most commonly the retroesophageal groove or mediastinum
- Patients with parathyroid gland(s) that are only minimally enlarged
- Patients with multi-gland parathyroid disease

Some surgeons routinely use ultrasonography in the operating room to confirm the findings of preoperative localization studies and mark the patient prior to sterile prep and incision [51].

Parathyroid Scintigraphy

Various methods of parathyroid scintigraphy have been used for preoperative adenoma localization. A trend seen in several imaging modalities for parathyroid pathology, multiple images are obtained at different times after administration of either contrast or a radionuclide, and the kinetics of perfusion of the parathyroid glands may help the interpreter to identify the parathyroid gland(s) of interest. One of the early applications of this rationale was ^{201}Tl thallous

Table 17.2 Summary of parathyroid localization studies

Modality	Advantages	Limitations	Radiation	Performance
Ultrasound	• Inexpensive • Portable units are available • Often located in offices where patients with 1° HPT are routinely followed (i.e. endocrinology)	• Highly dependent upon the experience of the operator • Ultrasonographically "silent" anatomic locations, i.e. retro-esophageal groove or the mediastinum • Multinodular thyroid disease • Patients with a short or thick neck • Limited sensitivity for small parathyroid adenomas • Limited sensitivity for multi-gland parathyroid disease	None	• Sensitivity: 70–96 % • Specificity: 50–100 % • Accuracy: 86.2–98 %
MRI	• May be useful for imaging of pregnant patients • Useful for identification of ectopic parathyroid glands	• Expensive • Limited sensitivity for small parathyroid adenomas • High-resolution machines are not available in many smaller facilities	None	• Sensitivity: 64–89 % • Specificity: 75–89 % • Accuracy: 64–84 %
Planar Scintigraphy	• Simple to interpret • Useful for identification of ectopic parathyroid glands	• Limited sensitivity for small parathyroid adenomas • Limited anatomic information • Time-consuming to perform	6.7–7.8 mSv	• Sensitivity: 54–88.2 % • Specificity: 87.8 % • Accuracy: 88.0 %
SPECT	• Improved localization and anatomic information compared to planar scintigraphy	• Limited sensitivity for small parathyroid adenomas • Limited sensitivity for multi-gland parathyroid disease	6.7–7.8 mSv	• Sensitivity: 74–87 % • Specificity: 84 % • Accuracy: 83.4–94 %
SPECT/CT	• Further improvement of localization and anatomic information beyond SPECT	• Large dose of radiation • Limited sensitivity for small parathyroid adenomas • Limited sensitivity for multi-gland parathyroid disease	18.4 mSv	• Sensitivity: 84.4–86 % • Specificity: 89.4–90.4 % • Accuracy: 78–88.8 %
4D CT	• Improved localization of ectopic parathyroid adenomas • Useful for identification of multi-gland parathyroid disease • Can detect parathyroid glands as small as 3 mm	• Large dose of radiation • Time-sensitive imaging protocol; technical errors can render results useless • False positives may be seen with vitamin D deficiency and multi-gland parathyroid disease	10.4–13.8 mSv	• Sensitivity: 92.1 % • Specificity: 95.6 % • Accuracy: 88.2–94.7 %
^{18}F-Fluorocholine-PET/CT	• May accurately localize lesions that were not identified using ultrasonography and/or sestamibi imaging • Lower radiation dose than SPECT/CT and 4D CT	• Expensive • Requires specialized facilities and equipment	5.2–6.7 mSv	• Sensitivity: 81–89 % • Specificity: 78 % • Accuracy: 80 %

chloride and ^{99m}Tc (technetium) pertechnetate dual-isotope scintigraphy, which was later replaced by dual-phase planar (DPP) scintigraphy using technetium-99 m sestamibi (Tc-99 m MIBI), which was more accurate [52]. In the case of ^{99m}Tc-sestamibi, the radionuclide becomes concentrated within the mitochondria of the metabolically hyperactive, adenomatous parathyroid glands. While the radionuclide tends to "wash out" of structures such as the thyroid gland and lymph nodes relatively quickly, it persists within the parathyroid tissue of clinical interest for longer time periods, allowing scintigraphic localization [16, 53].

SPECT

^{99m}Tc-sestamibi single-photon emission computerized tomography (SPECT) is a definite advancement, offering improved sensitivity and anatomic information compared to conventional parathyroid scintigraphy. Despite these facts, the sensitivity of SPECT is lacking in the detection of smaller adenomas (<250 mg) and multi-gland disease [54, 55].

SPECT/CT

SPECT/CT is a fusion study performed using ^{99m}Tc-sestamibi as the radionuclide and either a hybrid SPECT/CT gamma camera or software methods to assimilate the SPECT information with CT imaging. No difference in diagnostic accuracy has been noted between dual acquisition or software image fusion [56]. This study may be obtained as a single- or dual-phase study, with the first measurement being obtained at 5–15 min and the second measurement being obtained at 60–120 min after administration of the radionuclide. In dual-phase studies, the first portion will often include a diagnostic CT, while the delayed portion includes a nondiagnostic CT. The CT portion of the delayed imaging is necessary to ensure proper anatomic superimposition of the gamma imaging. While the second CT is a nondiagnostic, lower radiation study, it still adds to the overall radiation burden to the patient.

In an effort to quantify the improved localization for the additional radiation burden of the second part of this study, a comparison was made between the early phase of the SPECT/CT fusion by itself and the dual-phase study. Sensitivity, specificity, and accuracy were 84.8 %, 89.6 %, and 78 %, respectively, for dual-phase SPECT/CT. In comparison, early-phase SPECT/CT was found to have a sensitivity, specificity, and accuracy of 84.4, 89.4, and 76 %. These values were not significantly different for the study group of 75 patients, a finding which may prompt further evolution of this imaging technique [57].

Despite the proven advantages of fusion SPECT/CT, various forms of planar scintigraphy and SPECT are still used in the medical community. Investigation of this has identified a significantly higher rate of successful localization in high-volume parathyroid imaging centers (defined as centers annually performing more than 30 sestamibi scans for parathyroid localization) compared to low-volume centers. In the review of these cases, the authors noted that many of the patients with non-localizing studies obtained in the low-volume centers had undergone older imaging protocols [58].

4D Computerized Tomography

The accuracy of 4D computerized tomography (4D CT) in correctly localizing a parathyroid adenoma has been reported within the range from 88.2 to 94.7 % [47, 59–62]. Accurate identification of previously non-localizing parathyroid adenomas is of particular interest, and 4D CT has shown some promise in the pursuit of this, with successful identification of more than half of parathyroid lesions that failed to localize using ultrasonography and sestamibi [63]. In a direct comparison of imaging modalities, the overall diagnostic accuracy of 4D CT was found to be 94.7 %, as compared to 88.8 % for SPECT/CT

and 86.2 % for ultrasonography ($p<0.01$). Additionally, this study found 4D CT to have advantages in sensitivity, specificity, positive predictive value, and negative predictive value over the other two modalities [62]. Despite its accuracy in successful localization of a solitary parathyroid adenoma, the sensitivity and accuracy of 4D CT are somewhat compromised in cases of multi-gland disease [59, 61, 63].

One important concern that has been raised with 4D CT is the radiation exposure associated with dual-phase CT. The calculated effective radiation dose exposure from 4D CT varies based on equipment and imaging protocol and has been reported to be 10.4–13.8 mSv. While this radiation dose is greater than that of ^{99m}Tc-sestamibi-SPECT (7.8 mSv), it is less than the dose obtained from hybrid sestamibi-SPECT (18.4 mSv) [47, 64].

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has the advantages of the avoidance of ionizing radiation and excellent delineation of soft-tissue structures. In comparison to ultrasonography, MRI offers more adequate imaging of the mediastinum in the case of an ectopic adenoma. Typical characteristics for a parathyroid adenoma as seen on a gadolinium-contrasted MRI are T2 hyperintensity with contrast enhancement. Specialized MRI techniques, such as fat suppression, are available to meet specific clinical needs. In the case of parathyroid analysis, suppression of surrounding fat in the tracheoesophageal groove or mediastinum can help to make the gland more apparent than it would otherwise be. Even with the use of these techniques, the sensitivity and specificity of MRI in accurate diagnosis of diseased parathyroid glands are 84–89 % and 75–89 %, respectively [65].

4D contrasted MRI is a recently described parathyroid imaging tool. Multiparametric MR perfusion studies were found to accurately localize diseased parathyroid glands in 96 % of cases, and offered reliable differentiation of parathyroid glands from both thyroid tissue and lymph nodes [66]. To date, there has been no head-to-head comparison of 4D CT to 4D MRI described.

Despite the cost and diagnostic shortcomings of MRI as a tool for parathyroid localization, it may be the follow-up study of choice (after non-localizing ultrasonography) in clinical situations where avoidance of radiation exposure is particularly important, such as small children or pregnant women. Additionally, MRI may be an adjuvant worth considering in patients who have undergone previous neck surgery and did not localize using sestamibi-SPECT, as MRI may identify more than half of lesions that are missed by sestamibi in these patients [65].

Positron Emission Tomography

Positron emission tomography (PET) and PET-CT hybrid imaging studies have been used with great clinical success, particularly in the clinical staging of cancer, posttreatment cancer surveillance, and localization of unknown primary malignant tumors. The CT portion of a hybrid PET-CT is typically non-contrasted and the images are of greater slice thickness than those of diagnostic CT imaging studies, leading to a lower radiation dose. PET imaging may be performed using several tracers, including 5-fluorodeoxyglucose (^{18}F-FDG), ^{11}C-methionine, and ^{18}F-fluorocholine (^{18}F-FC). Up to this point, ^{18}F-FDG has failed to demonstrate sufficient sensitivity and accuracy to justify its use for parathyroid disease localization [67, 68]. ^{11}C-methionine has shown some (very limited) utility, but it is not readily accessible for widespread use [69]. ^{18}F-FC-PET/CT typically finds its use as a diagnostic tool in patients with prostate and hepatocellular carcinoma, but parathyroid adenomas have been incidentally noted in several patients. In patients who either failed to localize using conventional methods or had discordant findings on two conventional studies, ^{18}F-FC-PET/CT was found to accurately localize diseased parathyroid glands in more than 80 % of cases [51, 69].

Combined Imaging Modalities

Various combinations of preoperative localization techniques have been utilized in an effort to improve the success rate of MIRP. For example, the sensitivity of the combined findings of ultrasonography and SPECT/CT was 84 %, which was greater than the individual sensitivity of either study by itself [51]. In cases when concordance of findings is seen on these two imaging studies, some have advocated that intraoperative parathyroid hormone measurements are unnecessary [70, 71].

Surgical Adjuncts

Endoscopic Visualization and Magnification

Endoscopic techniques can allow for excellent visualization of the operative field while maintaining surgical access through a very small incision (15–20 mm). Magnification of structures up to 20× may be realized using an endoscope, while telescopic loupes generally offer 5.5–8.0× and conventional loupes usually offer 2.5–3.5× [72].

Intraoperative Radionuclide Guidance

Intraoperative nuclear mapping for parathyroid disease was first described by Martinez et al. in 1995 [11] and more definitively demonstrated by Norman and Politz in 2009 [17] to be effective in discriminating adenomatous parathyroid glands from other tissue types. ^{99m}Tc-sestamibi has a proclivity for localization within the mitochondria of hypermetabolic parathyroid tissue, such as that found within a parathyroid adenoma. A 20–25 mCu dose of ^{99m}Tc-sestamibi is administered intravenously 1.5–3 h prior to surgery. During the interim time period, planar scintigraphy imaging may be obtained, but is not necessary. After this time period, the radionuclide will sequester within the tissue of interest and, after the target gland is removed, a handheld gamma probe may be used to measure ex vivo radioactivity (counts per second) of the specimen in order to confirm with a high degree of accuracy that it is, in fact, a parathyroid adenoma. Gamma probe radioactivity measurements are a far more accurate predictor of cure than size, mass, or cellularity of the removed gland ($p < 0.0001$) [17]. It is fundamentally important to recognize that the gamma probe is not a "divining rod" that is placed into the surgical wound to point out the parathyroid adenoma—it is only useful for measurement of radioactivity once the specimen or a biopsy is excised.

Specimen radioactivity counts may only be meaningfully interpreted when expressed as a proportion of background radioactivity. In order to create this meaningful value, several measurements are systematically obtained using the gamma probe. It is the author's practice to have a member of the operating room staff available to document these measurements so they can later be formally recorded as part of the patient's medical record. In order to avoid confusion, an automated stamper is used to make 3 × 5 index cards with blank spaces for the pertinent values routinely obtained during MIRP (see Fig. 17.1).

In patients with a localizing sestamibi scan, gamma probe measurements showing radioactivity more than 20 % of the background have been clearly shown to be a reliable indicator of successful removal of a parathyroid adenoma. In the hands of high-volume parathyroid surgeons, the use of handheld gamma scintigraphy portends excellent results without identification of other glands, use of intraoperative frozen sections, or use of intraoperative PTH measurements [13]. A prospective study of 5000 patients undergoing treatment following this protocol found a successful cure in more than 99 % of patients. In all failures, a contralateral second adenoma was later identified as the cause. Analysis of counts and correlation to cure rate found radioactivity measures to be a more reliable indicator of cure than histology. Correlation of radioactivity counts to histologic findings definitively demonstrated the utility and reliability of this technique, with adenomas showing

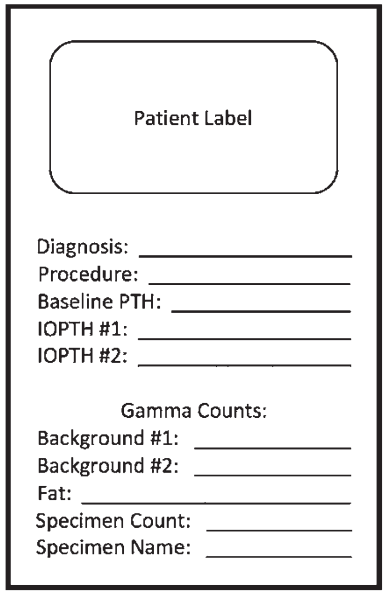

Fig. 17.1 Example of layout for 3×5″ index card stamp or printout for documentation during MIRP

57±38 % of background counts, hyperplastic parathyroid glands showing 16±4 % of background counts, normal parathyroid glands showing 4±0.1 % of background counts, and fat and lymph nodes always showing less than normal parathyroid glands [17].

Intraoperative Frozen Section Analysis

Microscopic analysis of a diseased parathyroid gland shows hypercellularity for both parathyroid hyperplasia and parathyroid adenoma. The main utility of frozen sections is to confirm that tissue is, in fact, parathyroid tissue in cases where this is unclear to the surgeon on gross examination. While this may be useful in select cases, up to a 94 % concordance between surgeon's gross examination and frozen section results has been noted [73], and the use of radionuclide gamma counts and intraoperative PTH measurement have allowed for more rapid and cost-effective confirmatory testing during parathyroid surgery in the majority of situations.

Intraoperative Parathyroid Hormone Measurement

In an effort to confirm biochemical cure of 1° HPT during MIRP, intraoperative PTH (IOPTH) levels may be measured prior to termination of the procedure. This is particularly useful in cases of multigland disease that were not identified preoperatively. If PTH levels remain inappropriately elevated after removal of the presumed offending parathyroid adenoma, the case is converted to bilateral neck exploration in an effort to identify other pathologic-appearing parathyroid glands.

This technique was first described in 1990 [74, 75] and has evolved since that time [76–79]. IOPTH testing is useful due to the relatively short half-life of intact PTH (~3–4 min), allowing measurement of a new steady-state PTH level shortly after removal of the offending gland. Two IOPTH levels are measured, one at 10 min after removal of the adenoma and another at 20 min. One of the most widely accepted standards are the modified Miami criteria (MMC), defined as an IOPTH value that is less than 50 % of the preoperative PTH value AND within the normal range [74, 77, 80–83].

The MMC have shown a sensitivity and specificity of 88 % and 22 %, respectively, for successful cure of 1° HPT [84]. A 10-year prospective study on the use of IOPTH in previously unexplored parathyroidectomy cases found a 93.4 % cure rate [85].

Drawbacks of IOPTH measurement include the time spent waiting on results and the potential for unnecessary bilateral neck exploration if PTH levels fail to decrease appropriately despite removal of a solitary offending gland. Commonly cited reasons for persistently elevated PTH after successful extirpation of a parathyroid adenoma are vitamin D deficiency [86, 87], renal dysfunction [78], and large body mass index (BMI) [44]. In vitamin D-deficient patients, the PTH levels decrease after removal of the adenoma, but may not satisfy the MMC. Renal excretion accounts for ~20–30 % of PTH clearance, leading to prolonged half-life of PTH. By measuring IOPTH at 15 and 25 min (instead of 10 and 20 min), 95 %

of patients with chronic renal insufficiency successfully met the MMC.

Some surgeons have recommended against routinely measuring intraoperative PTH levels during MIRP, citing successful preoperative localization combined with gamma probe measurements [13, 17] or concordance of two preoperative localization studies [70, 71] as sufficient to prove success.

One of the more recent technical developments related to IOPTH measurement involves equipment with a smaller footprint (for storage and use in the operative suite or operating room) and short time to prepare the specimen, run the assay, and report the result (as low as 8 min). Several platforms have been created specifically for this purpose.

Surgical Technique

A variety of protocols have been described as effective methods for performing MIRP with a high rate of success [5, 15, 17, 88]. This text is not intended to replace formal training or clinical and surgical experience, all of which are necessary for the appropriate patient selection and mastery of this operative technique. Beyond a baseline understanding of the surgical anatomy within the central compartment of the neck, the technical aspects are most similar to those used to perform lymphoscintigraphy and sentinel lymph node dissection, which is thought to require 20–40 supervised cases in order to achieve proficiency [5].

Preoperative Interdisciplinary Communication

Prior to bringing the patient to the operative suite, effective communication between the surgery and anesthesia teams can help to ensure that everything goes according to plan and optimal care is delivered. The authors routinely request the use of a monitored endotracheal tube and ask the anesthesia provider to place this under visualization using the Glide Scope® (Verathon; Bothell, WA, USA) to ensure optimal lead positioning. To assist with identification of the esophagus during surgery, an esophageal temperature probe is placed (anesthetist's preference as to whether or not this implement is actually used to monitor the patient). Preoperative medications include a single dose of intravenous acetaminophen (i.e., 4 g Ofirmev®; Mallinckrodt Pharmaceuticals, Dublin, Ireland), intravenous corticosteroids (i.e. 10 mg dexamethasone), and prophylactic intravenous antibiotics.

Operating Room Setup

Arrangement of equipment prior to MIRP allows for efficiency in performing each portion of the procedure, including endotracheal nerve monitoring, performing gamma measurements, and IOPTH measurement. Figure 17.2 demonstrates an example of an efficient operating room setup for MIRP. Discussion of patient positioning, including rotation of the surgical bed 180° toward surgeons, can help to ensure that the anesthesia team has all of the necessary equipment (i.e., anesthesia circuit extensions) to accomplish this. One consequence of turning the bed 180° is to allow easy access to the patient's distal lower extremities for IOPTH blood draws.

Patient Positioning

After the induction of anesthesia, the neck is placed in slight extension with a shoulder roll placed underneath the shoulders and the head is placed on a padded gel headrest with the back of the table elevated 30°.

Surgical Exposure and Approach

The surgical incision is marked as a 2 cm horizontal line at the midpoint between the cricoid and the sternal notch, as demonstrated in Fig. 17.3. The authors do not relocate the incision in any direction based on the presumed lateral anatomic location of the adenoma. Bovie electro-

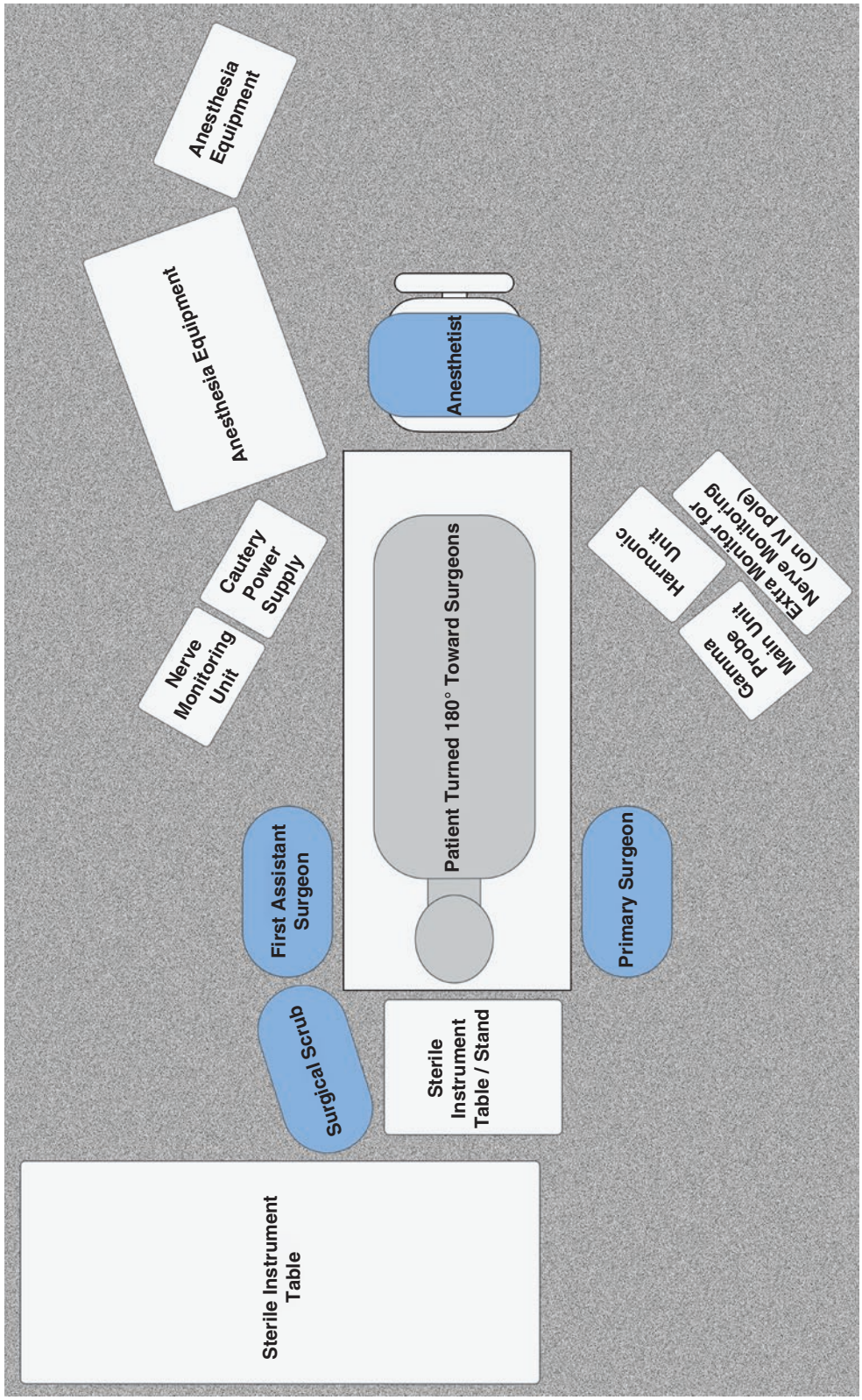

Fig. 17.2 Example of an efficient operating room setup for MIRP

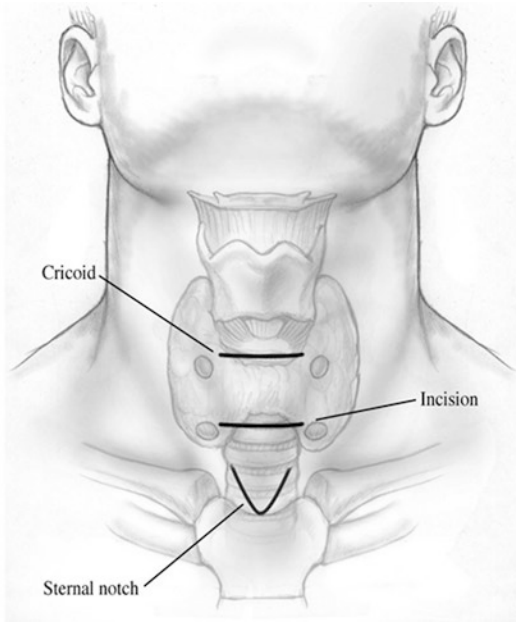

Fig. 17.3 The surgical incision is marked as a 2 cm horizontal line at the midpoint between the cricoid and the sternal notch [5] (used with permission from Elsevier/RightsLink)

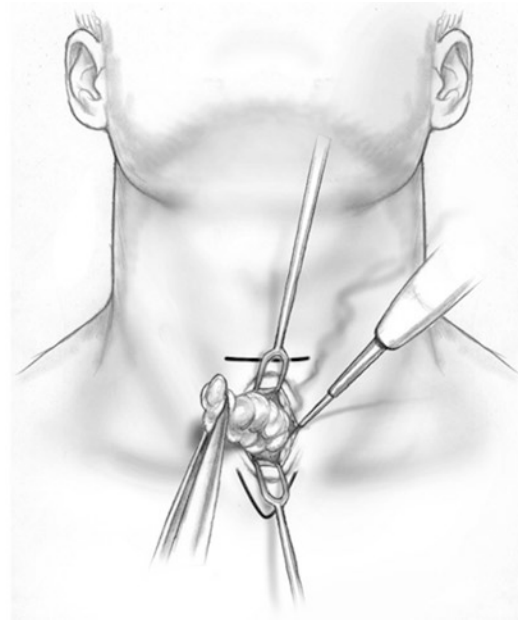

Fig. 17.4 A "dollop" of subcutaneous fat is excised from the central compartment to improve surgical exposure [5] (used with permission from Elsevier/RightsLink)

cautery is used to undermine the tissues in all directions down to the strap muscles to create a "dollop" of fat (see Fig. 17.4), which is removed and set aside for use as a negative control specimen during gamma probe radiation count measurements later in the procedure.

A self-retaining retractor is placed to provide adequate exposure of the surgical site, with the handle placed opposite to the side from the expected location of the adenoma. Strap muscles are divided in the midline and undermined toward the side of the suspected lesion using Bovie electrocautery, sweeping across the anterior face of the thyroid gland while exercising caution to avoid violation of the capsule or injury to associated vessels. Pretreatment of prominent vessels on the surface of the thyroid gland with bipolar cautery may help to prevent excess bleeding, which has the potential to "stain" the tissues within the surgical field, thereby compromising visual cues for the remainder of the case.

At this point, the ipsilateral thyroid lobe is manually palpated by the surgeon in order to identify any obvious pathology that would be appropriately addressed during the procedure. In addition, the anterior surface of the contralateral thyroid lobe is manually palpated, a maneuver that might influence the decision to perform bilateral exploration if any pathologic findings were to be encountered. The strap muscles are then retracted laterally, and a Kittner dissector is used to retract the thyroid lobe medially while a second dissector pushes laterally into the tracheoesophageal grove to give adequate visualization for parathyroid gland identification (see Fig. 17.5).

Identification and Removal of the Adenoma

Systematic blunt dissection is performed to identify the adenoma. The recurrent laryngeal nerve is not routinely identified. Hemostasis is maintained and small blood vessels are divided with bipolar cautery forceps or other power instrumentation. While using forceps to gain traction on the adenoma (as shown in Fig. 17.6), caution

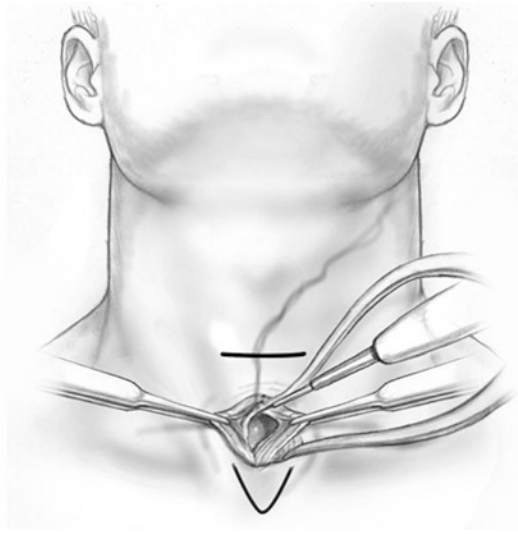

Fig. 17.5 The strap muscles are divided using Bovie electrocautery and the ipsilateral strap muscles are undermined and retracted laterally in order to allow for medial traction on the thyroid gland, thereby revealing the tracheoesophageal groove [5] (used with permission from Elsevier/RightsLink)

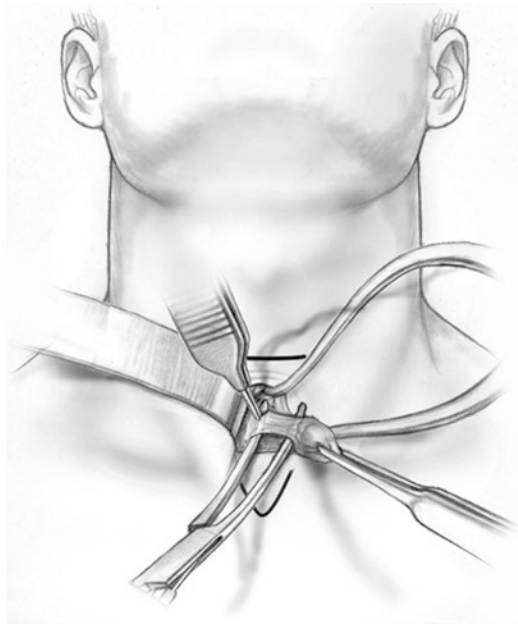

Fig. 17.6 A combination of blunt dissection and use of bipolar cautery are used to deliver the parathyroid gland while avoiding trauma to its capsule [5] (used with permission from Elsevier/RightsLink)

is exercised to avoid injury to its capsule. As the adenoma is retracted, blunt spreading and the harmonic scalpel (or bipolar cautery) are used to dissect the tumor from the surrounding soft tissue and to ligate its vascular pedicle.

Gamma Probe Techniques

One to two background radiation counts are obtained using the handheld gamma probe. These can be obtained from neutral zones over the patient's right shoulder and right supraclavicular area. The previously excised "dollop" of fat is measured as a negative control. The suspected adenoma is then measured ex vivo. In order to avoid spurious counts due to background radioactivity, measurements of the negative control and any specimens of interest are performed with the probe held facing toward the ceiling. Any excised tissue with radioactivity more than 20% of background is consistent with successful adenoma removal, in accordance with the "norman rule" [13].

Technical Considerations with Intraoperative PTH Measurement

Blood draws for PTH measurement are obtained at 10 and 20 min after gamma probe measurements suggestive of successful parathyroid adenoma removal. As previously mentioned, communication between teams can help the anesthetist to be prepared to obtain timely blood draws and avoid unnecessary delays. It may also be useful to warn the patient that blood may be drawn from veins in his or her feet during surgery, since this is a convenient point of access while maintaining a sterile field around the neck.

Prior to surgery, blood is drawn and PTH level is measured as a baseline value. PTH levels fluctuate, and measurements obtained prior to the day of surgery are not generally considered to be reliable baseline values for the purpose of IOPTH measurements.

The half-life of PTH is prolonged in patients with comorbid renal failure. Measurement of PTH levels at the usual 10 and 20 min may lead to falsely elevated PTH values and unnecessary

bilateral neck exploration. In order to avoid this, PTH levels can be measured at 15 and 25 min in patients with renal failure or a third measurement may be performed 10 min following the second measurement.

Wound Closure

Hemostasis is the obtained using bipolar cautery forceps, the wound is irrigated, a piece of Surgicel® (Ethicon, Cincinnati, OH, USA) or Surgicel® Fibrillar™ (Ethicon) absorbable hemostatic matrix is placed within the wound bed, and the strap muscles are re-approximated in their native midline position and tacked in place using a single figure-of-8 absorbable stitch. Finally, the skin edges are re-approximated in two layers and the incision is covered with Mastisol® adhesive (Eloquest Healthcare, Inc., Ferndale, MI, USA) and Steri-Strips® (3 M, St. Paul, MN, USA).

Making the Decision to Convert to Bilateral Neck Exploration

An important issue for any minimally invasive parathyroidectomy is the potential for conversion of the procedure to bilateral neck exploration in order to achieve a cure of the patient's primary hyperparathyroidism. There are many factors that may influence the decision to proceed with bilateral exploration, some of which may only be identified intraoperatively. Additionally, preoperative imaging, while often very helpful, is imperfect and plays only a partial role in identifying the need for bilateral exploration ahead of time. Many surgeons may place the surgical incision laterally and even perform a minimally invasive parathyroidectomy in a different manner from bilateral exploration. With the cervical incision placed in the midline, contralateral exploration is not a completely separate procedure after the first offending gland is removed [89].

There are at least four scenarios identified preoperatively that warrant bilateral neck exploration 100 % of the time: MEN syndrome, bilateral disease identified on localizing studies, history of lithium use, and known contralateral nodular thyroid disease [89]. Some advocate that bilateral exploration is warranted in patients under 25 years of age and pregnant patients [89], while MIRP has been successfully and safely utilized in these populations [31, 32, 40, 42].

With dual-concordant localizing imaging studies, conversion to bilateral exploration in order to achieve cure is 1–3 %, and is usually indicated by failure of IOPTH to decrease appropriately [70, 71]. In cases where imaging studies fail to localize any offending glands, the procedure may be initiated as exploration of one side of the neck followed by IOPTH measurement and exploration of the contralateral neck if the IOPTH fails to meet the MMC for cure.

Postsurgical Care

MIRP as an Outpatient Procedure

MIRP may be safely performed as an outpatient procedure in the vast majority of cases [46, 88, 90–92]. While uncommon, the decision to admit a patient to the hospital after MIRP may be made based on significant medical comorbidity, lack of a reliable caregiver, or the need to convert to bilateral neck exploration, among other reasons.

Hypocalcemia is the most common complication after parathyroidectomy performed in both the inpatient and outpatient settings, with reported incidence ranging from 0.28 to 7.0 % with adequate postoperative oral calcium supplementation [46, 90]. Calcium levels drop significantly during the first day following successful parathyroidectomy, and symptoms related to this occur most commonly during the first three days and may occur any time during the 2 weeks after surgery [45]. It has been the practice of some experienced physicians to routinely admit patients to the hospital for 1–3 days after parathyroid surgery, citing fear of untreated hypocalcemia leading to tetany [45]. Hypocalcemia rarely (0.2 %) necessitates the administration of intravenous calcium, and symptomatic hypocalcemia is most commonly ameliorated by increased intake of oral calcium tablets [46].

Patient Education

Effective patient education regarding postoperative expectations and early recognition of potential complications can save time and expense and may help to improve patient satisfaction. Patient education on the signs and symptoms of hypocalcemia is an important consideration, as recognizing these and increasing oral intake of calcium can often ameliorate symptoms and prevent unnecessary trips to the emergency department during the postoperative period.

Medications After Surgery

In addition to analgesics and antiemetics, patients are routinely prescribed oral calcium tablets after MIRP to prevent hypocalcemia, which may occur due to transient postoperative hypoparathyroidism or skeletal calcium uptake after correction of hyperparathormonemia. Patients and family members are counseled before surgery regarding the need for postoperative calcium supplementation. This is often confusing to patients, who may not understand the basis for calcium supplementation when their problem has been "high calcium levels" prior to surgery. The first dose of oral calcium should be taken within 3 h of the completion of surgery. Dosing instructions for oral calcium must be plainly stated to avoid mistakes in dosing. Some have even suggested to give the patient a bottle of calcium tablets and directions worded in terms of "number of tablets" instead of "number of milligrams of calcium." Several methods of determining an appropriate post-parathyroidectomy dose of oral calcium have been described [45, 91].

Calcium carbonate and calcium citrate are the most common formulations of oral calcium tablets. Bioavailability studies have shown dose-dependent absorption for both of these, with calcium citrate having significantly greater absorption for all doses [93]. While some surgeons have noted better patient tolerance of calcium citrate [45], other surgeons recommend calcium carbonate, as it is easily identified by patients as over-the-counter Tums® (GlaxoSmithKline, St. Louis, MO, USA) antacids.

Table 17.3 "8-Pack" of routine parathyroid laboratory tests

Calcium (total serum)	Magnesium
Calcium (ionized)	Phosphorus
PTH (intact)	Creatinine
25-Hydroxyvitamin D	Chloride

Postsurgical Follow-Up

In the author's practice, patients are routinely seen twice in the outpatient clinic setting after undergoing MIRP. The true postoperative clinic visit is scheduled 1–2 weeks after the date of surgery. Copies of the operative report and final pathology report are printed and physically given to the patient and any remaining Steri-Strips® are removed. An 8-pack (see Table 17.3) of parathyroid labs are obtained on the day of (and prior to) this appointment to identify any cases of post-parathyroidectomy hypocalcemia or persistent 1° HPT in order to facilitate appropriate planning and management. Any abnormality in the quality of the patient's voice is usually observed for at least 3 months after surgery, as the majority of minor voice complaints will resolve within this time [94]. Complaints that persist after the initial observation period warrant further evaluation, the details of which are beyond the scope of this text.

The usual time for the second and final outpatient follow-up appointment is scheduled for 1 year after surgery. An 8-pack of labs is obtained in conjunction with this appointment, as well. Any lab abnormalities (commonly vitamin D deficiency) are managed, as appropriate. The surgical incision is examined any further concerns that the patient may have after surgery are addressed, if necessary.

Summary

There is yet to be any broad consensus regarding the methods that are most effective in allowing for successful cure of 1° HPT using MIRP instead of the gold standard bilateral neck exploration with parathyroidectomy. There are imaging studies that successfully guide the surgeon in a large

majority of cases, but there is not a single study that is the "holy grail," offering reliable identification of not only a solitary adenoma, but also multiple adenomas and multi-gland hyperplasia. Several different perioperative techniques have been used (and in a variety of combinations) based on safety, cost, surgeon preference, availability of specialized equipment, and patient-specific factors.

Review of the extensive body of literature pertaining to minimally invasive parathyroidectomy demonstrates several important points that assimilate into a single conclusion. First, even the most reliable of parathyroid imaging studies available are imperfect and "successful" preoperative localization does not always indicate a surgical "slam dunk." Second, excellent results in curing 1° HPT may be offered to patients using several different preoperative and intraoperative algorithms for MIRP. Additionally, while the majority of parathyroid surgery in the USA is performed by low-volume parathyroid surgeons, the lowest complication rates and the highest rates of successful MIRP are realized by high-volume parathyroid surgeons. Finally, even the largest single-surgeon case reports in parathyroid surgery discuss failures of MIRP, conversion to bilateral neck exploration, and indications prompting this decision.

Society Guidelines: See other sections on indications for parathyroid surgery in general. None specific to radioguided parathyroid surgery [95].

Best Practices: N/A

Expert Opinion

Parathyroid surgery has advanced in recent decades largely due to precision preoperative imaging and less invasive surgical explorations and resections. Radioguidance is an extremely useful intraoperative adjunct for parathyroid surgery and is complementary to, but does not replace, intraoperative PTH assay measurement.

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Endoscopic Parathyroidectomy

18

William S. Duke, Paolo Miccoli, and David J. Terris

Contents

Introduction

Parathyroid surgery has changed significantly in the last two decades. Experience with conventional open bilateral neck exploration revealed that over 80 % of patients with sporadic primary hyperparathyroidism (PHPT) have disease due to a single abnormal gland [1]. This knowledge, combined with attempts to reduce the morbidity and improve the cosmetic impact of traditional parathyroid surgery, resulted in the development of more focused, minimally invasive parathyroidectomy techniques. These procedures were made feasible by advances in preoperative localization strategies and intraoperative adjuncts such as the intraoperative parathyroid hormone assay. Success with novel unilateral surgical techniques ultimately led to the development of endoscopic parathyroid procedures. Several variations of these approaches have been described, including purely endoscopic techniques requiring CO_2 insufflation of the neck and a unilateral video-assisted approach [2, 3]. The majority of endoscopic parathyroid surgery, however, is now performed using the open, minimally invasive video-assisted parathyroidectomy (MIVAP) technique described by Miccoli [4, 5], which is the focus of this chapter.

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Patient Selection

Proper patient selection is essential for successful endoscopic parathyroid surgery, and it has been suggested that specific criteria be strictly observed as surgeons begin to incorporate MIVAP into their practice [6]. The operation should initially be performed on patients with sporadic primary hyperparathyroidism, which reduces the likelihood of encountering multigland disease. An abnormal gland should be identified on at least one preoperative localization study to focus the initial dissection (Fig. 18.1), and that gland should be smaller than 3 cm. There should be no suspicion of parathyroid cancer, and the patient should not have thyroiditis or bulky thyroid disease, which might obscure visualization of the parathyroid gland(s) [6].

Since 80 % of patients presenting for parathyroid surgery having sporadic primary hyperparathyroidism due to a single adenoma [1], the majority of cases should be candidates for MIVAP. Most authors, however, report that fewer patients than expected are considered acceptable for MIVAP, with candidacy rates ranging from 37 to 78 % [7–10]. Patient eligibility for MIVAP depends not only on published selection criteria, but also on the prevalence of thyroid disease within a patient population, the reliability of preoperative imaging modalities in each specific institution, and the available of intraoperative parathyroid hormone (IOPTH) assays.

Eligibility will also depend on the surgeon's experience and comfort with the procedure. Over time, some surgeons have selectively expanded the inclusion criteria to include patients with intrathymic adenomas, multigland disease requiring bilateral surgery, presence of nodular thyroid disease, or prior contralateral neck surgery [6, 7, 11–13]. When the inclusion criteria are also expanded to include patients who have nonlocalizing or discordant imaging, the candidacy rate has been reported as high as 81 % [13].

Equipment

MIVAP can be performed with a limited number of instruments, many of which are already available in most operating rooms. A variety of general or customized retractors may be used to maintain the operative space, and an elongated, guarded electrocautery tip prevents inadvertent tissue injury in the narrow operative space. A blunt-tipped suction (Medtronic ENT, Jacksonville, FL) or 2 mm suction elevator facilitates dissection and prevents fogging of the endoscope. Small spatulas and atraumatic forceps are used to mobilize the adenoma, and cautery or vascular clips are used to ligate the vascular pedicle. The sine qua non of endoscopic parathyroid surgery, however, is a 30°, 5 mm, 29 cm long endoscope, which permits all members of the operating team to observe the operation on ergonomically placed monitors. With the exception of the vascular clips, all instruments required for MIVAP are reusable, which helps reduce the amortized costs of the procedure [14].

Operative Details

The ideal location for the incision is marked while the patient is sitting upright in the preoperative holding area. This ensures that the final scar will be concealed in the most favorable naturally occurring skin crease [15]. The patient is then positioned supine on the operating table. The neck is gently extended, and no shoulder roll is used. The procedure may be performed under local or general anesthesia [6]. General anesthesia permits the use of a laryngeal electromyographic (EMG) endotracheal tube if laryngeal nerve monitoring is desired. The operating table may be rotated 180° so the patient's lower extremities are facing the anesthesia team. This facilitates access to the patient's foot veins for peripheral blood acquisition in order to pursue IOPTH assessment and obviates the need for an arterial line. The surgeon repeats an ultrasound once the patient is in the final surgical position to help guide the subsequent dissection [16].

The primary surgeon generally stands at the patient's right side. The camera operator is positioned on the patient's left, and another assistant stands at the patient's head and retracts to maintain the operative space. A monitor is placed at each side of the patient's head to give all members of the surgical team an ergonomic view of the operative field [17].

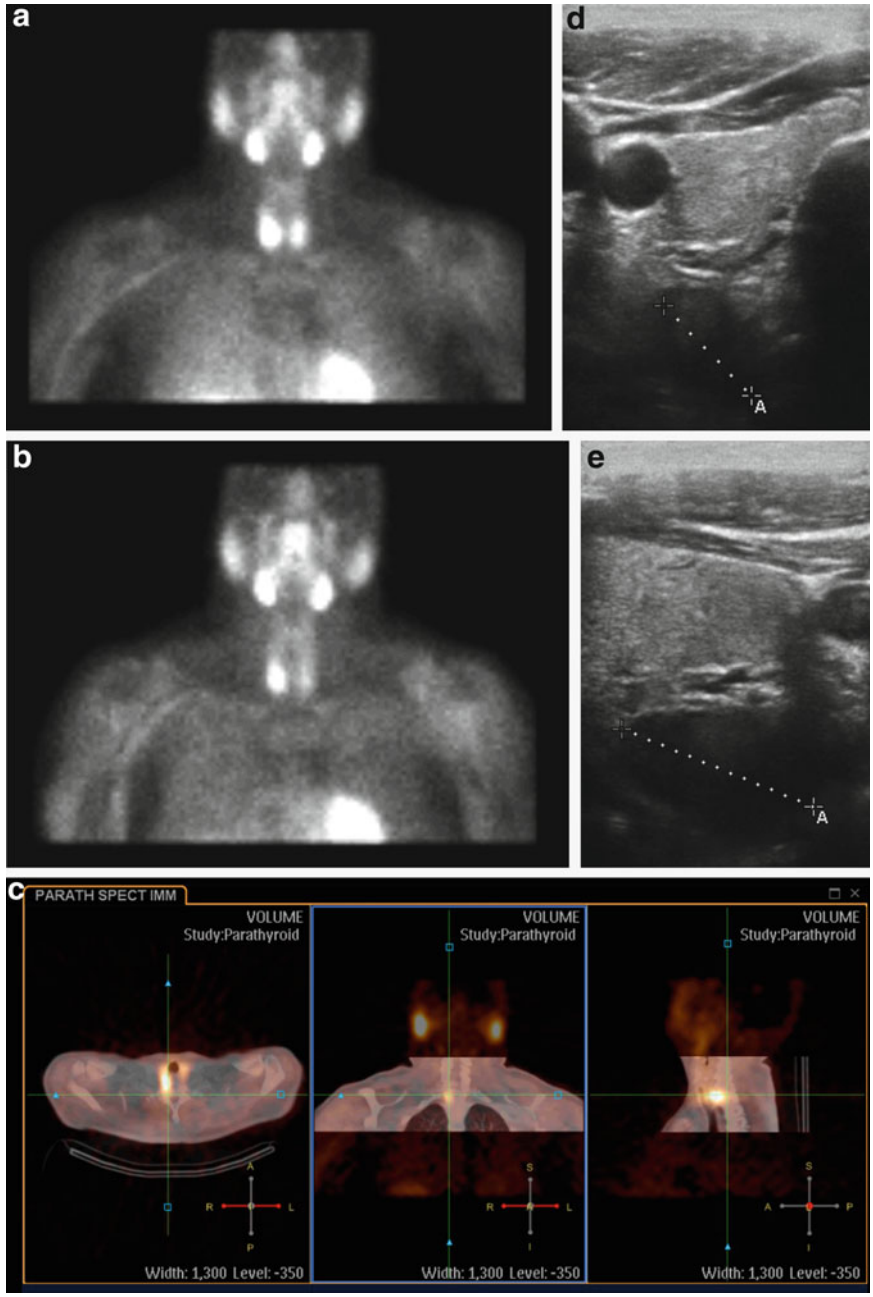

Fig. 18.1 Preoperative imaging studies in candidate for minimally invasive, video-assisted parthyroidectomy. Early (**a**) and delayed (**b**) Tc-99m-sestamibi and SPECT-CT images (**c**) suggesting a parathyroid lesion posterior to the inferior pole of the right thyroid. These were concordant with transverse (**d**) and longitudinal (**e**) ultrasound images, which revealed a hypoechoic lesion posterior to the right lower thyroid

The operation begins by creating a 1.5–2.0 cm incision in the center of the previously identified cervical crease [18, 19]. The midline location improves the cosmetic outcome, permits easy access to both sides of the neck, and can easily be extended if conversion to a conventional parathyroidectomy is required [18]. Once the incision is complete any identifiable platysma fibers in the midline are divided transversely, preserving the anterior jugular veins, and the midline "linea

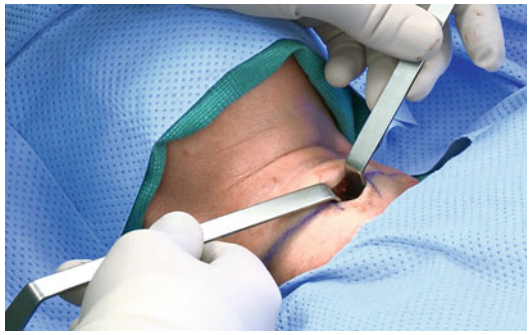

Fig. 18.2 Proper placement of the retractors to maintain the operative space during minimally invasive, video-assisted parathyroid surgery

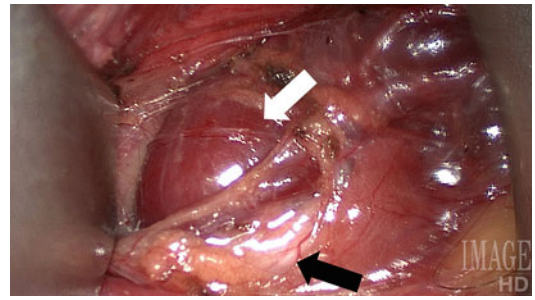

Fig. 18.3 Endoscopic view of the parathyroid adenoma (*white arrow*) corresponding to the lesion seen in Fig. 18.1. The location deep to the recurrent laryngeal nerve (*black arrow*) confirms it to be an overly descended superior adenoma. The retractors are distracting the carotid sheath structures (*left*) and thyroid gland (*right*) to maintain the operative space

alba" between the strap muscles is identified. No subplatysmal flaps are required. The strap muscles are separated with a combination of electrocautery and blunt dissection until the thyroid isthmus is identified. The muscles are then bluntly elevated off the thyroid gland on the side of the suspected adenoma, and dissection continues laterally and posteriorly until the posterior aspect of the thyroid gland and the carotid sheath are visualized.

Proper positioning of the retractors is imperative to ensure adequate visualization of the operative space (Fig. 18.2). The lateral retractor distracts the strap muscles and carotid sheath structures, while the medial retractor "hooks" the thyroid gland. Ventral and medial traction on the thyroid lobe retracts and elevates the lobe, further opening the operative pocket and facilitating dissection of the peri-thyroidal fibrofatty tissue.

Once the operative space has been exposed, the endoscopic portion of the procedure begins. While one assistant maintains the operative space with retractors, the camera operator introduces the endoscope through the incision. The endoscope is held with the 30° lens directed dorsally and inferiorly for most of the procedure. The tip of the scope can be rotated upward if dissection high in the neck is required. For mediastinal dissection, the camera operator moves to the head of the bed to angle the endoscope into the chest. Two hands are used to steady the endoscope and reduce image tremor [7].

Using primarily blunt dissection, the region of the suspected adenoma is gently explored. Any bleeding could stain the surrounding tissues or obscure the endoscopic view, so attention to absolute hemostasis is crucial. While not always necessary, identifying the recurrent laryngeal nerve (RLN) helps protect it from injury and serves as a landmark for the depth of dissection. Inferior parathyroid glands are always ventral to the coronal plane of the RLN and superior glands are dorsal to the nerve (Fig. 18.3) [20].

Identification of the parathyroid gland(s) is enhanced by the magnified endoscopic visualization. If the adenoma is not encountered in the expected location, the medial retractor can be repositioned to ensure that the gland was not inadvertently captured under the retractor blade. Once the abnormal gland is identified it is bluntly freed from the surrounding tissue and the vascular pedicle is ligated with either clips or an energy device, taking care to avoid injuring the RLN or violating the capsule of the gland. IOPTH levels are assessed according to the surgeon's preference. The surgeon may wish to halt the operation after removal of the abnormal gland or examine the other ipsilateral gland. If the IOPTH levels fail to decrease appropriately or if inspection of the second gland suggests multigland disease, a contralateral exploration for the remaining parathyroid glands can be performed through the same incision in the manner described above [18].

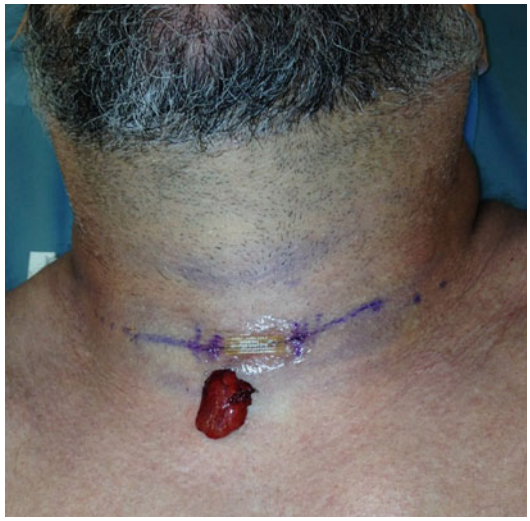

Fig. 18.4 Excised parathyroid adenoma from Fig. 18.3 and wound closure

Once all abnormal parathyroid tissue is removed, hemostasis is obtained and half-sheet of Surgicel (Ethicon, Inc., Somerville, NJ) is placed into the wound bed. The strap muscles are either reapproximated in the midline with a single 3-0 Vicryl (Ethicon, Inc., Somerville, NJ) figure-of-eight suture or left open. Retraction on the small incision may traumatize the skin edges, which are therefore trimmed so that fresh tissue is available for wound closure [21]. The subcutaneous tissue is closed with buried interrupted 4-0 Vicryl sutures and the skin edges are sealed with DermaFlex adhesive (Chemence Medical Products, Inc., Alpharetta, GA) and a single transverse Steri-Strip (3M Corporation, St. Paul, MN) (Fig. 18.4). No drains or external sutures are required [22–24]. Deep extubation is performed whenever possible to limit coughing or bucking that can occur on emergence from anesthesia with an endotracheal tube in place.

Outcomes

Cure Rate

Successful MIVAP requires proper patient selection, surgeon skill and experience, and appropriate use and interpretation of perioperative adjuncts such as imaging techniques and the IOPTH assay. When these elements are combined, cure rates with MIVAP have been shown to equal or exceed the 95 % success rate with traditional bilateral neck exploration [11]. In one of the few published comparisons of MIVAP versus traditional four-gland exploration, Del Rio et al found no differences in the recurrence rates between the two approaches (2.6 % vs. 3.7 %, respectively) [25]. Other authors have consistently reported cure rates higher than 97 % when MIVAP is performed on patients with localizing imaging studies and with use of IOPTH assessment [6, 8, 14, 26, 27].

Routine use of IOPTH assessment significantly improves the cure rate and decreased the operative time in minimally invasive parathyroid surgery, including MIVAP, when compared to unilateral open surgery without IOPTH assessment [28]. The sensitivity of IOPTH in MIVAP is 97 %, with a specificity of 88 %, a positive predictive value of 99.6 %, and an accuracy of 97 % [29]. Barczyński et al found that using IOPTH directly improved cure rates in minimally invasive parathyroid surgery from 91 to 99 % [28], and is especially beneficial in patients with only one positive preoperative localization study [11, 28]. IOPTH assessment in MIVAP also decreases the inadvertent removal of physiologically normal parathyroid glands, and may contribute to the decreased incidence of hypocalcemia seen in MIVAP when compared to conventional bilateral neck exploration [26].

Cosmetic Outcome and Patient Satisfaction

The cosmetic benefit of MIVAP is one of its greatest advantages and one of the main reasons the procedure was developed. It is commonly performed through a 1.5 cm incision [8, 30], with minimal tissue disruption. In a retrospective series comparing MIVAP to open minimally invasive parathyroid surgery, Barczyński et al found that MIVAP was associated with a shorter scar and higher patient scar satisfaction [31], and in a randomized study comparing MIVAP and open

surgery patients these differences persisted for at least 6 months after surgery [26]. In Miccoli's prospective randomized trial of MIVAP versus bilateral neck exploration, significantly improved cosmetic outcomes were observed in patients undergoing MIVAP [32]. Casserly et al also reported smaller scars and improved scar ratings in their MIVAP group (mean 1.7 cm), compared with bilateral neck exploration (mean 4.3 cm) [19]. These improved cosmetic outcomes were confirmed in a large systematic review of video-assisted minimally invasive parathyroid surgery by Lombardi et al [11]. The small scar and minimal dissection in MIVAP also results in less pain and lower use of pain medication after surgery [7, 11, 26, 31].

Complications

Recurrent Laryngeal Nerve Injury

Recurrent laryngeal nerve injury in MIVAP is uncommon, with transient injury reported in up to 3 % of cases and permanent injury in 0.8 % of cases [6, 9, 27, 30, 31, 33]. These low rates compare favorably with conventional bilateral neck exploration, and are likely due to the magnified visualization of the RLN afforded by the endoscope as well as the limited extent of dissection around the nerve [11, 33].

Hypocalcemia

Conventional bilateral parathyroid surgery results in transient postoperative hypocalcemia in approximately 12 % of patients; this rate increases to 25 % if biopsy of the glands is performed [26, 31]. Permanent hypocalcemia occurs in up to 2.3 % of patients after bilateral exploration [34]. This risk of hypocalcemia is reduced in focused minimally invasive procedures such as MIVAP, when only one gland is exposed. Transient hypocalcemia after MIVAP is reported in 2.5–11 % of cases [6, 9, 14, 27, 30, 31], while permanent hypocalcemia occurs in no more than 0.4 % of patients [30]. Unilateral parathyroid surgery is also associated with less severe hypocalcemia and a lower postoperative calcium requirement than conventional surgery [34].

Conversion

Conversion from MIVAP to an open exploration may occur in up to 14 % of patients [7–10, 12, 14, 30, 35]. Reasons for conversion from a focused video-assisted exploration to either open or bilateral video-assisted exploration include inability to locate the abnormal gland, difficult dissection, intraoperative suspicion of malignancy, concurrent thyroid goiter that limits exposure, concern for multigland disease or an ectopic gland, and failure of the IOPTH levels to drop appropriately or IOPTH assay malfunction [7, 8, 30]. Miccoli et al has reported on the feasibility of performing a video-assisted bilateral neck exploration without IOPTH assessment [18]. This procedure is performed using the same incision and surgical technique as a focused MIVAP. Bilateral MIVAP risks removing physiologically normal enlarged glands, but it may be beneficial when IOPTH assessment is not desired or available [18].

Cost

An early criticism of MIVAP was that it was more expensive than both conventional bilateral surgery and open minimally invasive procedures [7, 31]. These cost differences were attributed to the additional endoscopic equipment, requirement for preoperative imaging studies, and the longer operative time when these procedures were initially implemented. Subsequent studies, however, have shown that MIVAP now is generally less expensive than conventional surgery [33].

Most operating rooms now have the equipment to perform endoscopic procedures, and the camera system used for MIVAP is the same as that used for laparoscopy [14]. The equipment used for MIVAP is reusable, which further reduces costs over time [14]. Many patients have imaging studies performed before they are sent to the surgeon, and these therefore do not contribute

directly to the cost of the procedure [27, 33]. Preoperative ultrasound is beneficial in localizing the adenoma and therefore helping to shorten the operative time, and may also detect concurrent surgical thyroid disease, which can be addressed at the time of the parathyroidectomy [27].

Operative Time

Some authors have suggested that MIVAP takes longer to perform than open parathyroidectomy approaches, but these differences were either less than 5 min or the studies were heterogeneous and not sufficiently powered to detect operative time differences [31, 36]. Once the learning curve of approximately 30 cases has been surpassed, most authors report that MIVAP is associated with a faster time to adenoma identification and a shorter overall operative time than open techniques, even when IOPTH assessment is used [7, 8, 11, 28]. Most authors now report that MIVAP can routinely be performed within 30 min [8, 14]. While some of the improvements in MIVAP operative times are likely related to improved surgical proficiency with experience, reductions in operative time are also related to improvements in the processing speed of IOPTH assays, which can now be accomplished more rapidly than frozen section analysis [25, 28, 37].

Summary

Most cases of sporadic primary hyperparathyroidism are caused by a single abnormal gland, and therefore a majority of patients should be amenable to treatment that does not require bilateral neck exploration and dissection of all four parathyroid glands. The minimally invasive video-assisted parathyroidectomy technique targets only the hyperfunctional gland, and was developed to reduce the amount of dissection and risk associated with conventional parathyroid surgery, and to improve the cosmetic impact of surgical intervention. In appropriately selected patients, the cure rate with MIVAP equals or exceeds that of conventional four-gland exploration, and is associated with reduced postoperative hypocalcemia, decreased pain, and improved cosmetic outcomes.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion
Most patients with primary hyperparathyroidism and at least one positive preoperative localization study are candidates for endoscopic surgery. The minimally invasive video-assisted parathyroidectomy approach, when coupled with intraoperative assessment of parathyroid hormone levels, has a cure rate that equals or exceeds that of conventional four-gland exploration.

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Unilateral Neck Exploration for Primary Hyperparathyroidism

19

William S. Duke

Contents

Introduction

Conventional parathyroid surgery requires a large transverse cervical incision and bilateral neck exploration (BNE) with exposure of all four glands. While highly successful, this procedure results in a long scar, and the extensive dissection occasionally risks significant postoperative hypocalcemia. Though some conditions still require bilateral surgery, the majority of patients with primary hyperparathyroidism (PHPT) have a single hyperfunctional gland. Increased understanding of this pathophysiology, along with advances in preoperative imaging modalities and intraoperative adjuncts, have led to the development and successful implementation of minimally invasive, unilateral neck exploration (UNE). This approach improves the cosmetic and physiologic outcomes of parathyroidectomy without compromising the cure rate achieved by conventional surgery.

Development of Unilateral Parathyroid Surgery

Since the time of the first recorded parathyroid operation nearly 100 years ago, BNE with exposure and visual or frozen section examination of all four parathyroid glands has been considered the gold standard for parathyroid surgery [1, 2].

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This procedure was deemed necessary because, prior to the advent of preoperative parathyroid imaging modalities and intraoperative parathyroid hormone assays, there was no other way of determining which or how many parathyroid glands were hyperfunctional, and the now-familiar distribution pattern of abnormal glands in PHPT was unknown [2, 3]. Bolstered by long-term cure rates of 95 %, BNE became the mainstay of surgical management of PHPT. Decades of subsequent experience with BNE revealed that 80–85 % of patients with PHPT have single-gland disease, with 15–20 % of cases due to multigland disease and 1 % due to parathyroid carcinoma [4].

Though BNE continued to be widely practiced by most parathyroid surgeons into the 1990s [3], it was not without limitations. The operation classically required a large neck incision, extensive dissection, and prolonged inpatient management, and was associated with a number of complications, including postoperative hypocalcemia [1, 5]. Additionally, visual inspection of the parathyroid glands, even when augmented by frozen section analysis, could not completely discount the possibility of multigland disease [2].

As it became recognized that the majority of patients with PHPT have a single hyperfunctional gland, options for less invasive procedures that would maintain the high level of cure achieved with BNE while reducing operative morbidity were explored. Advances in preoperative localization modalities allowed surgeons in the 1980s to begin testing the concept of more limited parathyroid surgery [2, 6]. Further refinements in imaging and surgical techniques and continued technological milestones, such as the development of intraoperative parathyroid hormone (IOPTH) assays, helped revolutionize parathyroid surgery in the late 1990s and lead to widespread adoption of focused, unilateral surgery. The consequent reduction in surgical morbidity and improved management strategies resulted in increased surgical referrals for patients with PHPT [7].

Defining Unilateral Parathyroid Surgery

The nomenclature of parathyroid surgery has always been ambiguous. Even when BNE was the only operation performed, some surgeons relied on gross assessment of the glands' appearance, while others performed biopsy and frozen section analysis of each gland [2]. Characterizing more limited parathyroidectomy options is even more challenging, with a recent study identifying over 75 different definitions of minimally invasive parathyroid surgery in the literature [8]. Unilateral parathyroid surgery can be limited to identification and removal of only the abnormal gland, or can involve exposing the second ipsilateral gland for visual inspection or frozen section analysis [2]. The exploration can be guided by palpation, imaging, or a hand-held gamma probe [2]. Complete unilateral exploration, in which both ipsilateral glands are examined, initially represented a compromise between conventional bilateral exploration and focused, single-gland surgery, theoretically decreasing the risk of undetected multigland disease while reducing the operative time and leaving the contralateral neck undisturbed [9]. Incorporating IOPTH assessment as a surgical adjunct has been shown to further improve outcomes in UNE, even in the setting of a normal appearing second ipsilateral gland [10].

Regardless of how the operation is performed, UNE, as the name implies, differs from BNE in that the dissection only occurs on one side of the neck. While UNE is considered "minimally invasive" compared to BNE, over the last decade there has been increasing debate about what constitutes true "minimally invasive" parathyroid surgery. Some authors have proposed incisions length restrictions [11], while others have suggested that minimally invasive surgery requires more than just a small scar [12]. Regardless of how the operation is perceived or classified, the fundamental goals and advantages of UNE compared to traditional BNE are to reduce the

cosmetic impact of surgery by shortening the incision [13], decrease the operative time [6, 9, 13], improve postoperative pain and hasten the recovery process by reducing the dissection [1], and decrease operative risk by limiting the number of parathyroid glands exposed [1].

Selection Criteria for Unilateral Parathyroid Surgery

Candidates for UNE must meet two criteria: they must have primary hyperparathyroidism due to suspected single-gland disease, and there must be some guidance as to the location of the hyperfunctional gland on at least one preoperative imaging study [14, 15]. Preoperative imaging studies are not obtained to determine a patient's eligibility for surgery, but rather to determine the most appropriate operation to perform [16]. While a number of localization modalities are available, the majority of patients receive either a Tc-99m-sestamibi (sestamibi) scan, a high resolution cervical ultrasound, or both (Fig. 19.1) [16, 17].

Even though up to 85 % of patients with PHPT are potentially eligible for unilateral parathyroid surgery [2, 9], the actual candidate pool is reduced to 65–83 % of patients by limitations associated with preoperative localization techniques [9, 10]. Sestamibi scans, in particular, can have a sensitivity as low as 50 % in some centers [9, 18]. These rates improve significantly when the imaging is performed in high-volume specialty centers, where up to 80–90 % of patients may have localizing sestamibi scans [18, 19]. Localization can also be improved when imaging studies are combined. Single-gland disease has

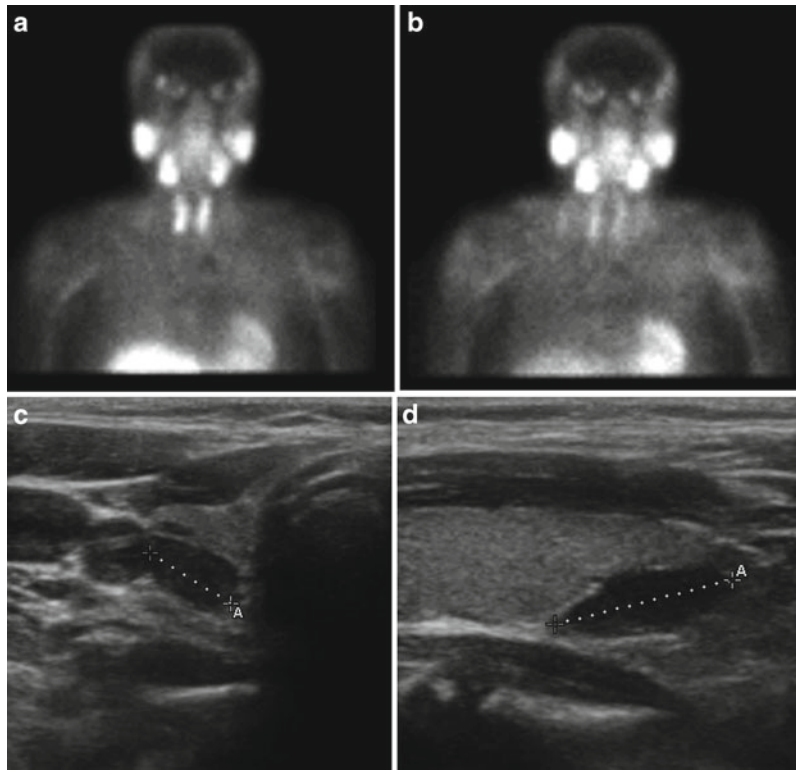

Fig. 19.1 Preoperative imaging for a patient undergoing unilateral parathyroid surgery. Early (**a**) and delayed (**b**) Tc-99m-sestamibi scans showed slightly more persistent uptake in the right inferior central neck. These findings were concordant with the transverse (**c**) and longitudinal (**d**) ultrasound images, which revealed a hypoechoic lesion posterior to the lower portion of the right thyroid

been confirmed in up to 96–99 % of patients who have concordant (colocalizing) sestamibi and ultrasound studies, while up to 17 % of patients with discordant imaging have multigland disease [1, 20].

Some authors perform unilateral surgery when the ultrasound and sestamibi results are concordant [14, 20], while others will perform a UNE if at least one study indicates which side to explore first [15, 20]. Patients with discordant or nonlocalizing studies should be considered for BNE [20]. Patients at risk for multigland disease, including those with familial or syndromic causes of HPT (MEN syndromes), secondary or tertiary HPT, or a history of lithium use, should undergo planned bilateral exploration [3, 21].

Operative Steps

As mentioned previously, numerous operative variations have been described for unilateral parathyroid surgery. Minimally invasive radioguided and endoscopic parathyroid surgery are specifically addressed elsewhere in this text, so the procedure described in this chapter will focus on open unilateral surgery without gamma probe or video assistance.

Reducing the scar size and improving the cosmetic outcome of parathyroid surgery is one of the advantages of unilateral surgery. Therefore, careful attention is given to planning the incision length and location. Marking the incision site while the patient is sitting up in the preoperative holding area ensures that the scar will be concealed in the most favorable naturally occurring skin crease [22]. Most open unilateral explorations can be performed through midline incisions less than 4 cm, with many authors routinely reporting incision lengths of 2–3 cm [11, 18, 23]. In addition to being more cosmetically favorable, a midline incision permits exploration of the contralateral neck should conversion to a bilateral exploration be required [24].

The procedure can be accomplished with the patient sedated [23] or under general anesthesia. General anesthesia permits intraoperative recurrent laryngeal monitoring, if desired. The patient is positioned supine on the operating table with minimal or no neck extension. Rotating the table 180° so the patient's lower extremities are facing the anesthesia team allows IV access in the patient's foot for IOPTH assessment. Once the patient is in the final operative position, a surgeon-performed ultrasound is used to confirm the location of the suspected adenoma and guide the subsequent dissection [25]. The incision site is then infiltrated with an epinephrine-containing anesthetic solution. The skin is incised and the platysma is divided. Subplatysmal flaps are not necessary [25]. The strap muscles are separated in the midline, exposing the thyroid isthmus. Care is taken to maintain absolute hemostasis, as any bleeding from superficial tissue layers can obscure the critical visualization of deeper structural details. Attention is then directed to the side of the neck predicted by preoperative imaging to harbor the hyperfunctional parathyroid tissue. The strap muscles are bluntly elevated off the anterior and lateral aspect of the thyroid. The thyroid is then retracted medially, taking great care not to conceal a parathyroid gland under the retractor blade, and the process of identifying the abnormal gland(s) begins.

Most parathyroid glands reside in predictable locations in the central neck [26]. Guided by the preoperative imaging, and using meticulous technique, the surgeon begins searching for the most likely abnormal gland. The superior glands are more constant in location. They are usually found behind the superior aspect of the thyroid gland near where the recurrent laryngeal nerve passes under the inferior constrictor, within a 2 cm area centered 1 cm cranial to the junction between the recurrent laryngeal nerve and the inferior thyroid artery [27], and are always dorsal to the plane of the recurrent laryngeal nerve. The location of the inferior parathyroid glands is more variable. They are typically located within 1 cm of the inferior aspect of the thyroid gland, anterior to the plane of the recurrent laryngeal nerve, but may be intimately associated with the thymus or thyrothymic tract in up to 26 % of patients [26, 27].

The superior gland is revealed by retracting the thyroid gland ventrally and medially, exposing the posterior aspect of the thyroid lobe and

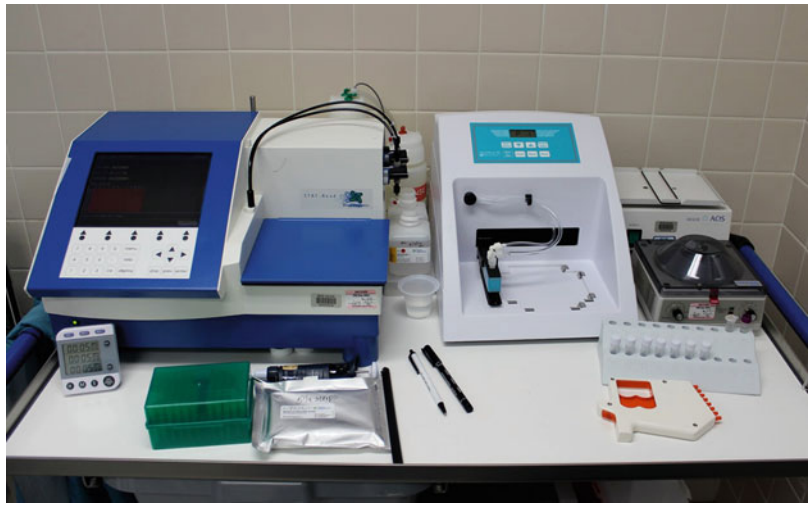

Fig. 19.2 Intraoperative parathyroid hormone assay equipment (Future Diagnostics, Wijchen, Netherlands)

the paratracheal region. This exposure can usually be accomplished without disrupting of the middle thyroid vein. Occasionally, however, the middle thyroid vein and superior pole vessels will need to be divided to fully access this space. The inferior parathyroid gland may be found by gently dissecting the soft tissue just below the inferior pole of the thyroid gland, or it may be identified dorsal to the gland by gentle retraction of the thyroid lobe.

Surgeons must be able to visually distinguish a normal from abnormal parathyroid gland. Normal parathyroid glands are typically flat, with a light brown to tobacco color, and measure 3–8 mm long with an average weight of 40 mg [27]. They are usually surrounded by or capped with fat. Parathyroid adenomas are typically larger, more rounded, rubbery, and a darker red-brown in color.

The presence of an enlarged parathyroid gland may be heralded by areas of fullness or bulging of the peri-thyroidal fat [3]. Gently spreading the surrounding fat may help reveal the enlarged gland. Once identified, blunt dissection is used to separate the adenoma from the surrounding soft tissue, until only the vascular pedicle remains attached to the gland. Soft tissue adherent to the capsule of the gland may be grasped to facilitate retraction and dissection, but care should be taken to avoid grabbing or excessive manipulation of the gland itself, as this may rupture the gland or stimulate release of stored parathyroid hormone and alter subsequent IOPTH levels [28]. The vascular pedicle feeding the adenoma is then either transected with electrocautery or ligated with vessel clips and sharply divided if it is near the recurrent laryngeal nerve.

Though not uniformly performed by all authors [6, 10], complete UNE implies that after removal of the parathyroid adenoma identified on preoperative imaging, the second ipsilateral gland is identified and sometimes biopsied [9, 14, 24]. The decision to perform a complete unilateral dissection or terminate the operation after identifying only one adenoma depends on the surgeon's philosophy, the preoperative imaging, and the availability of IOPTH assessment (Fig. 19.2). Some surgeons feel that if preoperative imaging studies, especially when concordant, match the operative findings, the operation can be concluded after removing the adenoma (with or without identifying a second ipsilateral gland), and that further assessment is not necessary [9]. Other authors suggest that identification of a second, normal gland still requires biochemical confirmation (using an IOPTH assay) that all the hyperfunctional parathyroid tissue has been removed [10]. In cases where a second gland cannot be identified or appears abnormal, or when the IOPTH levels fail to decrease appropriately,

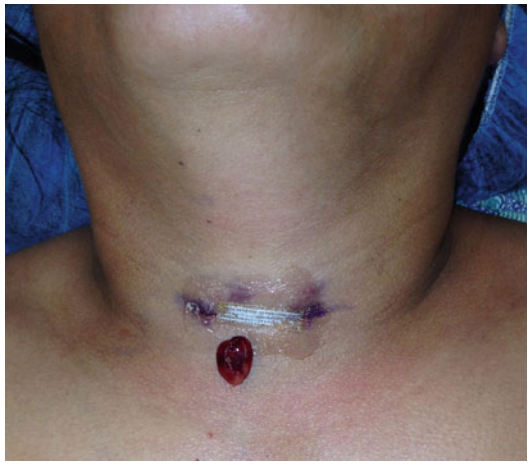

Fig. 19.3 Right inferior parathyroid adenoma, corresponding to the lesion seen on the Tc-99m-sestamibi scan and ultrasound in Fig. 19.1. The right superior parathyroid gland was normal

bilateral exploration is warranted [10]. The procedure on the contralateral side is performed through the same incision in an identical manner as the initial side, with a goal of identifying all four parathyroid glands (see following chapter).

Once all the hyperfunctional parathyroid tissue has been removed, the surgical field is irrigated, hemostasis assured, and half a sheet of Surgicel (Ethicon, Inc., Somerville, NJ) is placed into the wound bed. The strap muscles are either reapproximated in the midline with a single 3-0 Vicryl (Ethicon, Inc., Somerville, NJ) figure-of-eight suture [29] or left open. The subcutaneous tissue is closed with buried interrupted 4-0 Vicryl (Ethicon, Inc., Somerville, NJ) sutures and the skin edges are closed with tissue adhesive and a single transverse Steri-Strip (3M Corporation, St. Paul, MN) (Fig. 19.3). No drains or external sutures are required [29–31]. Patients are generally discharged on the same day of surgery with an oral calcium regimen [32, 33].

Outcomes

Cure Rate

The reported cure rate of 96–98 % after unilateral parathyroid surgery is identical to that of bilateral exploration in appropriately selected patients [6, 9, 14], and has been shown to be durable [34]. While some authors do not routinely perform an IOPTH assay in unilateral surgery, others have shown improved outcomes when this assessment is utilized [1, 10]. Rajaei et al. evaluated the second ipsilateral gland in 809 patients, and found that 13 % of procedures would have resulted in failure if assessment of the second gland alone was used to determine the presence of multigland disease, while the cure rate for UNE with IOPTH assessment was 98.5 % [10]. IOPTH assessment, which can now be performed in the operating room in as little as 8 min [35], has been specifically recommended in cases where localization studies are discordant or only one study is performed [1].

Conversion

Conversion to bilateral surgery occurs in 6–14 % of planned unilateral explorations [10, 14, 15]. These conversions typically result from failure of the IOPTH levels to drop appropriately, concern over multigland disease after inspection of the second ipsilateral parathyroid gland, failure to identify the desired gland(s), or other unexpected but concerning intraoperative findings [10, 14, 15].

Recurrent Laryngeal Nerve Injury

Recurrent laryngeal nerve injury is uncommon in parathyroid surgery, and is almost always transient. Temporary injury occurs in 4 % of cases, with permanent vocal fold paresis reported in only 0.4 % of patients having any minimally invasive parathyroid surgery [5, 6]. These rates compare favorably to the temporary and permanent rates of nerve injury in conventional bilateral parathyroid surgery (2 % each) [5, 6].

Hypocalcemia

Although transient hypocalcemia may occur in up to 5 % of patients undergoing any minimally invasive parathyroid surgery [6], a randomized controlled trial of unilateral neck exploration resulted in no hypocalcemic episodes in 47

patients [6]. In contrast, temporary and permanent hypocalcemia occur in up to 25 and 2%, respectively, of patients after bilateral exploration [1, 6]. The hypocalcemia after unilateral surgery tends to be less severe than after bilateral surgery, with a higher calcium nadir and a decreased need for postoperative calcium replacement [6].

Operative Time

Two studies have directly compared operative times in unilateral and bilateral parathyroid surgery. In both studies the mean operative time was shorter in unilateral exploration (60 vs. 87 min; 72 vs. 82 min) [6, 9], though the difference was significant in only one study [9].

Summary

The majority of patients with primary hyperparathyroidism have single-gland disease. Unilateral neck exploration, in which only one or two ipsilateral parathyroid glands are exposed, is therefore a feasible option for most patients with this disease. Candidates for unilateral surgery should not have conditions associated with multigland disease, such as multiple endocrine neoplasia, renal hyperparathyroidism, or a history of lithium use. Additionally, at least one preoperative imaging modality should identify the most likely side of the hyperfunctional gland. Unilateral neck exploration is performed through a small midline incision that is cosmetically favorable and allows for easy conversion to bilateral surgery, if necessary. After identifying and excising the abnormal gland, visual inspection or frozen section analysis of the second ipsilateral gland or intraoperative parathyroid hormone assessment can be used to determine if the operation can be successfully terminated or if further exploration is warranted. In appropriately selected patients, the cure rate of unilateral surgery equals that of traditional bilateral neck exploration, with a decreased risk of postoperative hypocalcemia.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion
Successful unilateral parathyroid surgery depends on the surgeon's understanding of the patient's disease and their ability to diagnose primary hyperparathyroidism due to single-gland disease. Surgeons who perform unilateral explorations must also be able to accurately interpret preoperative imaging studies, recognize normal and abnormal glands, and be well-versed in intraoperative parathyroid hormone assay interpretation.

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Bilateral Neck Exploration for Primary Hyperparathyroidism

20

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Contents

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Introduction

Primary hyperparathyroidism (pHPT) is a disease that can be managed surgically with excellent outcomes. In previous years, the gold standard surgical approach was bilateral neck exploration with identification of all parathyroid glands in order to distinguish between patients with single-gland disease versus those with multigland disease. In the last decade several adjuncts have been developed that can limit neck exploration. Preoperative imaging, intraoperative PTH (IOPTH), and radioguided techniques have allowed surgeons to offer unilateral or focused parathyroidectomy. While postoperative outcomes show this to be an excellent option for some patients, others may not be candidates. Those with a family history of parathyroid disease (for example—multiple endocrine neoplasia I and II) and those with imaging suggestive of multigland disease should be offered bilateral exploration. In addition, some patients undergoing unilateral parathyroidectomy will have persistent or recurrent disease necessitating bilateral exploration. For these reasons, the parathyroid surgeon who offers the unilateral approach should be adept at both techniques. We acknowledge that use and availability of adjuncts and thus surgical approaches in pHPT is highly variable from surgeon to surgeon. Adjunct test performance statistics are beyond the scope of this

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chapter. We will specifically focus on the indications and technical considerations of bilateral exploration.

Indications for Bilateral Neck Exploration

Should Bilateral Exploration Always Be Performed?

There are some surgeons that believe all patients with pHPT should undergo a bilateral exploration. There are several arguments for this approach (Table 20.1). Large volume experiences from centers that routinely perform four-gland exploration find a higher rate of multigland disease than those performing unilateral exploration [1, 2]. Since extent of parathyroidectomy is typically governed by intraoperative PTH kinetics, this suggests that additional abnormal glands are present in some patients despite appropriate reduction in IOPTH. The natural history of these additional glands is unclear. The results of those patients undergoing unilateral parathyroidectomy are excellent and show that this approach is reasonable for patients with nonfamilial pHPT and imaging studies suggestive of single-gland disease [3, 4]. However, Norman and colleagues have published the largest series of bilateral vs. unilateral exploration with results in over 15,000 patients [2]. The authors used a gamma probe to confirm the presence of parathyroid tissue and do not use IOPTH. With a mean follow-up of 6 years in all patients, unilateral exploration yielded a persistent/recurrence rate of approximately 5 % while recurrences in those undergoing bilateral exploration were <1 %. Further, over 20 % of bilaterally explored patients had greater than 1 gland removed compared to 3 % of those undergoing unilateral exploration. The data suggest bilateral exploration is very effective intervention in pHPT patients. Based on the data, the authors abandoned unilateral exploration. Subsequent correspondence regarding this paper pointed out that the authors did not use IOPTH, which guides extent of parathyroidectomy for many parathyroid surgeons [3]. Further, the definitions of persistence/recurrence were not clear. Thus, whether there is improved long-term durability in favor of bilateral exploration is unknown at this time and additional data from multiple centers with long follow-up (>10 years) is needed to determine which set of patients benefit from one approach over the other. Despite these controversial issues, for patients with pHPT who have an appropriate drop in intraoperative PTH after unifocal exploration will have at least excellent short term (<5 year) outcomes. Since only the ipsilateral side has been dissected, contralateral dissection at a later time point is not hindered in case of a recurrence.

Table 20.1 Advantages of unilateral versus bilateral exploration in pHPT

Unilateral	Bilateral
Reduced operative time	All parathyroid tissue visualized
Less dissection required with reduced operative risks including bleeding and injury to RLN	Rates of persistent/recurrent pHPT may be lower compared unilateral
Unexplored contralateral side easily accessible if second operation required	More likely to identify familial disease

Conversion of Unilateral to Bilateral Neck Exploration

For those surgeons who prefer the unilateral approach and use IOPTH, exploration begins on the side suggestive of the adenoma on imaging (typically ultrasound or sestamibi scanning). Figure 20.1 is a flow diagram demonstrating decision making for those who may be candidates for unilateral exploration. If only one abnormal gland is identified and the intraoperative PTH drops to an appropriate level, then the operation is terminated. Some surgeons examine the ipsilateral gland in order to evaluate for multigland disease. If an additional enlarged gland is identified and/or the PTH value remains inappropriately elevated, then the remaining parathyroid

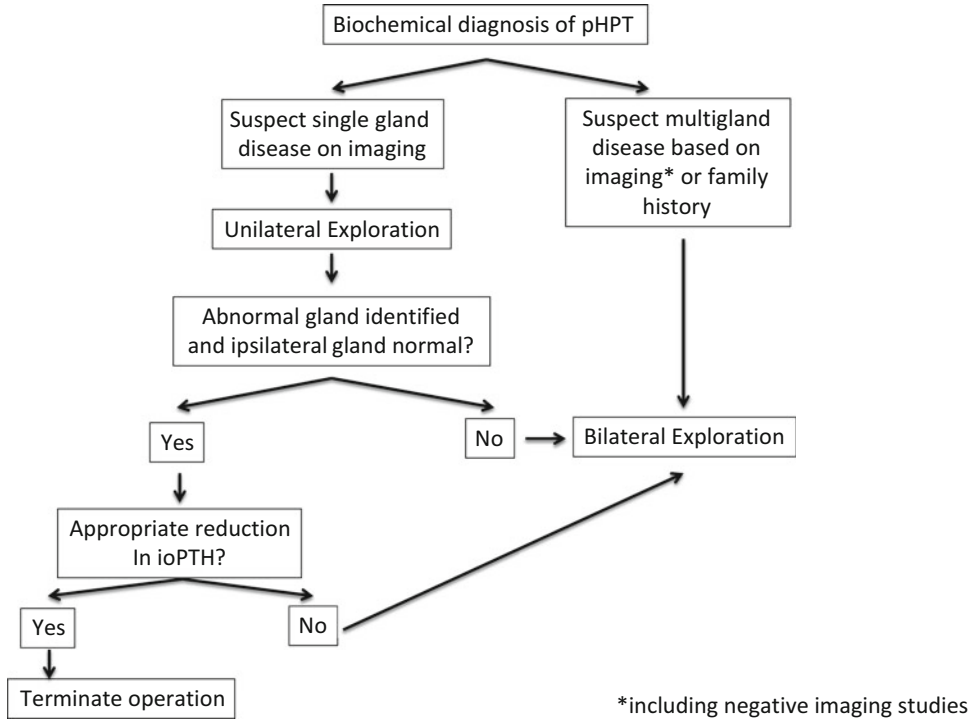

Fig. 20.1 A flow diagram demonstrating the indications for bilateral exploration for surgeons that offer unilateral exploration. *ioPTH* intraoperative parathyroid hormone monitoring

glands on the contralateral side are explored. Once a diagnosis multigland disease is established, the remaining parathyroid glands should be identified but not yet resected. If four-gland hyperplasia is present and three-and-a-half-gland parathyroidectomy (subtotal parathyroidectomy) is carried out, the most abnormal/enlarged glands should be resected first, leaving a 50-100 mg remnant. The remnant should be marked with a stitch or clip as these patients may have germline defects driving parathyroid proliferation and will be at risk for recurrence.

Imaging Suggestive of Multigland pHPT

In rare instances, imaging will suggest multigland involvement in pHPT. These patients are not candidates for the unilateral approach and should undergo bilateral exploration and four-gland examination. Multigland disease is thought to occur in 10–20 % of patients with pHPT [5, 6]. In any suspected case of multigland disease, all parathyroid glands should be exposed and examined with an intraoperative determination of extent of parathyroidectomy. However, it is rare to identify mutligland disease on preoperative imaging. A consistent finding among multigland pHPT patients is nonlocalizing preoperative imaging [7]. The reasons for this are unclear but may be related to gland size in multigland disease. Any patient with subtle multigland findings or nonlocalizing findings on imaging should be considered for bilateral exploration. Intraoperative PTH testing can still serve as an adjunct to visual inspection and can help determine extent of resection.

Familial Hyperparathyroidism

Patients with germline mutations in the MENIN (MEN1) or RET gene (MEN2A) are at high risk

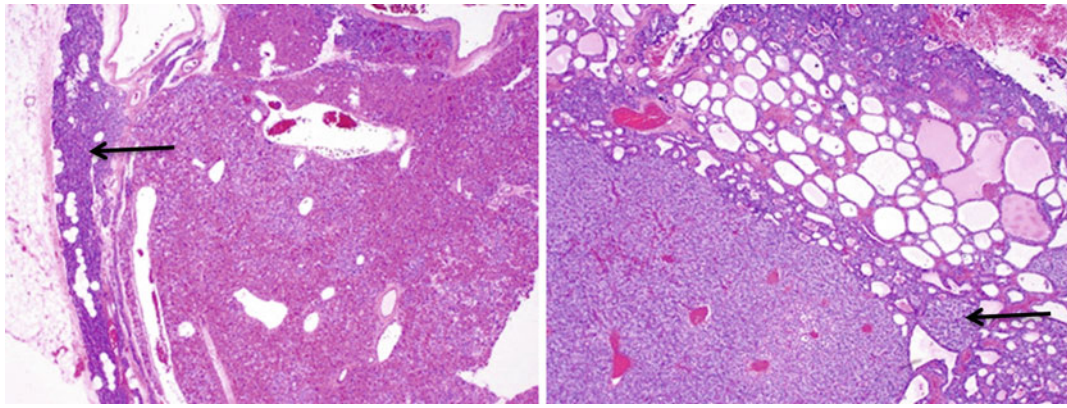

Fig. 20.2 H+E sections from patients with primary hyperparathyroidism with either adenoma or hyperplasia. (**a**) Parathyroid adenoma, abutting normal parathyroid gland. *Arrow* indicates rim of normal parathyroid tissue. (**b**) Parathyroid hyperplasia demonstrating hyperplastic nodularity seen in patients with multigland disease. *Arrow* indicates nodularity adjacent to a large hyperplastic component

for pHPT and multigland disease. Indications for surgery are similar to that of nonfamilial disease. However, familial patients are at much higher risk of developing recurrent disease since they have a germline driver of parathyroid growth. Thus, all parathyroid cells in these patients can be considered abnormal. This is demonstrated by H+E staining of parathyroid glands from patients with adenomas versus those with hyperplasia (i.e. multigland disease) (Fig. 20.2). Parathyroid adenomas occur as a single focus of neoplasia, associated with somatic mutation events. This can be seen histologically as the hypercellular adenoma abutting normal parathyroid tissue. In contrast, hyperplastic glands, or those associated with familial syndromes, have changes throughout the gland with noted nodularity of hyperplastic cells and an absence of normal gland architecture.

MEN1 is a common cause of familial hyperparathyroidism. The most common initial presentation of these patients is hypercalcemia and elevated PTH levels [8]. Although a family history of parathyroid disease is commonly discovered at the initial clinic visit, in some cases the parathyroid surgeon may not be not be aware of the patient's familial syndrome prior to operation. Any patient found to have multigland pHPT should be considered for MENI and medical genetics referral. The surgical approach to these patients includes bilateral exploration, identification of all four parathyroid glands and a cervical thymectomy in case of an ectopic or supernumerary parathyroid gland located in the thymus. It should be noted that ectopic/supernumerary rests of parathyroid tissue are relatively common given the embryology of parathyroid glands (discussed below) and in familial cases this tissue can be a source of persistent or recurrent disease after exploration. Subtotal parathyroidectomy (or three-and-a-half-gland parathyroidectomy) has been advocated over total parathyroidectomy with forearm autograft for these patients to reduce the severity of postoperative hypoparathyroidism and hypocalcemia [9]. Notably, familial patients are at risk of recurrent pHPT given their germline mutations. If a patient has undergone a subtotal parathyroidectomy and has recurrent disease/symptoms, the second operation can have additional challenges. First, these patients are undergoing redo neck surgery, which can lower rates of success depending on the degree of scar tissue. Second, partial resection of a parathyroid remnant with an unpredictable blood supply can place the new parathyroid remnant at risk. For these reasons some surgeons prefer to perform cryopreservation of parathyroid tissue in case of postoperative hypoparathyroid-

ism. We generally take a conservative approach to initial parathyroidectomy in MEN1 patients and operate when symptoms and hypercalcemia absolutely require intervention.

MEN2A patients (mutations in the *RET* gene) also manifest hyperparathyroidism. However, these patients are also at risk for medullary thyroid carcinoma, which generally guides timing of thyroidectomy and neck exploration. Because total thyroidectomy can affect parathyroid blood supply and the phenotype of hyperparathyroidism is thought to be less severe in MEN2A, a more conservative approach to parathyroidectomy can be employed [10]. Different *RET* mutations in MEN2A carry different recommendations for timing of prophylactic thyroidectomy. When young children and infants with MEN2A undergo thyroidectomy, special consideration must be given to the parathyroids and these operations are often performed in relatively high volume centers. Recent experience suggests a conservative approach to parathyroidectomy during prophylactic thyroidectomy is warranted [11].

Persistent or Recurrent pHPT After Unilateral Neck Exploration

In some cases, the initial parathyroid operation fails to reduce PTH and calcium levels. Persistent pHPT is distinguished from recurrent pHPT by elevated calcium levels less than 6 months after neck exploration. To avoid permanent hypoparathyroidism, a thorough review of the patient's course should be undertaken. Prior to repeat neck exploration, the previous operative reports and imaging studies should be studied in detail. Pathology of all removed tissue should be reviewed. Patients in this setting are at higher risk of permanent hypoparathyroidism since previous operations likely removed parathyroid tissue. Every attempt should be made to preserve normal parathyroids in the reoperative setting. A bilateral approach is appropriate to carefully identify all remaining parathyroids followed by an appropriate resection (subtotal for hyperplasia, resection of a single adenoma). Intraoperative PTH can also assist with extent of resection. Repeat neck operations can result in high morbidity (cranial nerve injury, bleeding, and hypoparathyrodism) and for this reason some surgeons will repeat localization studies or perform 4D CT in an attempt to localize abnormal parathyroid glands [12].

Operative Approach

Conduct of the Operation

Bilateral exploration begins similar to the unilateral approach. After skin incision and subplatysmal flap elevation, the strap muscle fascia is divided in the midline and the strap muscles are dissected off the thyroid gland. If an abnormality is identified on preoperative imaging then the suspected parathyroid gland is targeted as a first step. The thyroid is retracted medially to expose the TE grove and undersurface of the thyroid gland. Once the targeted gland is identified, then a search for the ipsilateral gland is performed. No parathyroid tissue is resected at this point and care is taken to preserve the blood supply of the two parathyroid glands. Attention turns to the contralateral side and the parathyroid glands dissected. After all four glands are exposed and examined, a decision is made regarding extent of resection. If a single or double adenoma is present, then the abnormal parathyroid gland or glands are resected. If all four glands are enlarged (multigland disease), then the goal is to resect parathyroid tissue to leave a 50–100 mg remnant. Typically the remnant is marked with permanent suture. Even in the most experienced hands, parathyroid glands can be difficult to identify, as they can appear a similar color to thyroid parenchyma or paratracheal lymph nodes. A low threshold for frozen section is reasonable given the relatively good accuracy of frozen section for parathyroid tissue. A very small section of parathyroid gland can be removed with a scalpel, taking care not to damage the in situ gland. Retaining an adequate volume of parathyroid tissue cannot be understated as permanent hypoparathyroidism and the resultant hypocalcemia can result in significant lifestyle changes for the patient. Patients

with permanent hypoparathyroidism can be treated with daily PTH injections, but long-term effectiveness and safety profiles are still under investigation.

Embryology of Parathyroid Glands and Approach to the Missing Gland

The location of parathyroid glands can be variable from one patient to the next [13]. This is dictated by developmental biology and the migration of the parathyroid glands from the third pharyngeal pouch (inferior parathyroid glands and thymus) and the fourth pharyngeal pouch (superior parathyroid glands) during embryogenesis. As the third pouch descends past the fourth pouch to reach the upper mediastinum/lower neck the parathyroid glands can be deposited anywhere along the migration track. As a result, parathyroid glands can be found in the thymus, the carotid sheath, in the retroesophageal space, the thyrothymic ligament, and rarely within the thyroid parenchyma. Since the goal of the bilateral exploration is to identify all parathyroid tissue, the parathyroid surgeon should have a systematic approach to identify a gland not in a typical location (posterior to the thyroid gland). If a missing gland is suspected, then the remaining three glands should be identified and preserved. The tracheoesophageal groove on the side of the missing gland is carefully examined followed by the thyrothymic ligament. Most glands can be found in this location. If a thorough dissection is not productive, attention then turns to the retroesophageal space. Palpation can also be employed to augment visual inspection. Intraoperative ultrasound can be used to evaluate for an intrathyroidal parathyroid gland, but can be challenging in the setting of thyroid nodularity and the possibility of false positives must be considered. If the gland remains missing after these maneuvers, then a decision should be made about the need to identify the remaining gland versus completing the operation. If single-gland disease has been identified and no other disease is suspected, then the operation is terminated. In these cases, we find it useful to use intraoperative PTH as an appropriate PTH reduction can increase confidence that the procedure has been successful. Not all surgeons use intraoperative PTH, but in this instance it can guide the extent of operation. Some surgeons also advocate a routine or select radioguided approach, using preoperatively injected sestamibi. The gamma probe can then be used during the operation to identify parathyroid tissue. In any case, if the missing gland is thought to be pathologic, then continued dissection is warranted. An ipsilateral cervical thymectomy is performed and dissected ex vivo to look for the gland. The last step is to open the carotid sheath. The contents of the carotid sheath include the vagus nerve (supplying motor fibers to the recurrent laryngeal nerve), the carotid artery, and the jugular vein. Parathyroid glands have been identified as high as the angle of the mandible, most often requiring a separate incision. In addition, some parathyroid glands have been found in the chest, in a location inaccessible from a neck incision. If the gland cannot be identified and thought to be pathologic, consideration should be given to closing the incision with a plan to re-image the patient with additional modalities or proceed with a different operative approach (radioguided parathyroidectomy).

Summary

Bilateral neck exploration is an appropriate approach to patients with pHPT and is important in the absence of intraoperative PTH monitoring to identify patients with multigland disease. The parathyroid surgeon who performs unilateral exploration should have defined thresholds (intraoperative PTH, ipsilateral-gland morphology) for converting to a bilateral approach to manage multigland disease. An understanding of parathyroid embryology is critical to performing a bilateral exploration when a gland cannot be identified in a usual anatomical location.

Society Guidelines: The AAES is currently writing new guidelines and the last set is from 2005.

Best Practices: N/A

Expert Opinion

Parathyroid disease management approaches are diverse across institutions and surgical practices. Long-term outcomes in patients selected to undergo unilateral or bilateral exploration are excellent and a surgeon should use approriate imaging and intraoperative tests specific to the experience of their institution and practice. Bilateral exploration remains an important component of parathyroid surgery particularly for those patients with confirmed or suspected multigland disease.

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Surgical Management of Known Multiglandular Parathyroid Disease

21

Daniel Clayburgh and Maisie Shindo

Contents

Introduction

The majority of patients presenting with hyperparathyroidism have a single adenoma responsible for elevated parathyroid hormone levels. However, in about 10–15 % of cases, two or more parathyroid glands are involved in the disease process. Thus, any surgical intervention must address all diseased glands in order to provide benefit to the patient. While multiglandular disease is commonly sporadic, multiple other factors may lead to gland enlargement, including drugs such as lithium, renal disease, and genetic disorders such as multiple endocrine neoplasia; in these instances significantly more investigation and/or treatment is required than in those patients with sporadic disease. Thus, the clinician must carry a heightened level of suspicion for other causes of disease when multiglandular disease is recognized.

Given that preoperative imaging and localization studies are often not accurate in predicting the glands involved in multiglandular disease, bilateral parathyroid exploration is often required in these cases. The parathyroid surgeon must have a thorough understanding of the anatomy and potential ectopic locations of the parathyroid glands, as well as the potential locations of supranumerary glands that may sometimes be encountered. A full discussion of parathyroid anatomy is contained elsewhere in

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this book and falls outside the scope of this chapter. However, multiple options for the extent of surgery are available to deal with multiglandular disease, and may be tailored specifically to the individual patient and underlying disease process. This underscores the importance of a thorough preoperative evaluation and determination of the underlying cause of multiglandular hyperparathyroidism.

Basic Surgical Techniques in Multiglandular Parathyroid Disease

Fundamentals of Parathyroid Exploration

An understanding of parathyroid anatomy is paramount in bilateral parathyroid exploration for multiglandular disease. The surgeon must have knowledge of the typical locations, ectopic locations, and parathyroid blood supply. This has been thoroughly discussed in earlier chapters. When performing bilateral exploration, each gland should be assessed to determine if it is normal or abnormal in size, and its vascular blood supply should be identified. One should resist the urge to excise the gland as soon as it is identified and exposed. It is important to treat every parathyroid gland as if it is the last one left in the patient.

Subtotal Parathyroidectomy

Once identified, a small fragment of the gland should be biopsied at the tip of the gland away from the polar vessels to confirm parathyroid tissue. If four gland exploration is planned, unless the intent is for total parathyroidectomy, all four glands should be identified first and the decision for which gland will be left in situ should then be made after assessing viability and location. If the surgical strategy is for subtotal parathyroidectomy, approximately 5 × 10 mm size of the most viable appearing gland should be left in situ. A healthy parathyroid should not be pale, which indicates arterial insufficiency, nor dusky, which is indicative of venous congestion. When choosing between viable parathyroid glands to leave in situ, it is best to leave the inferior glands, as they are located more anterior and thus more accessible for re-excision with less risk to the recurrent laryngeal nerve in the event of recurrent hyperparathyroidism

Total Parathyroidectomy with Autotransplantation

Total parathyroidectomy and autotransplantation is appropriate for patients with secondary hyperparathyroidism who are not candidates for transplant, since regrowth of parathyroid tissue left in the neck is likely to occur from the stimulus of chronic uremia. Re-implantation is typically in the brachioradialis muscle, ideally the nondominant arm; however, these patients often have an arteriovenous shunt for dialysis access in their nondominant arm. Often a suitable site for reimplantation can be located at a point in the arm far from the shunt, but if that is not possible, reimplantation will need to occur in the contralateral arm.

Cryopreservation

Permanent hypoparathyroidism is a devastating complication of parathyroidectomy. This risk is significantly higher in patients undergoing subtotal or total parathyroidectomy. Despite the use of autotransplantation after total parathyroidectomy, a small percentage of patients may not have full function of the autotransplanted tissue and experience hypoparathyroidism. To combat this complication, the technique of cryopreservation was developed in the 1970s [1]. This technique involves preserving one or more resected parathyroid glands at -80 °C for later autotransplantation. This is described in more detail in another chapter. Autotransplantation after cryopreservation generally has a lower rate of success than primary autotransplantation, with graft success rates ranging from 17 to 83 % [2]. While this technique is widely used as “insurance” against

poorly functioning autografts, given the poor functioning of cryopreserved tissue and the relative rarity of permanent hypoparathyroidism after parathyroidectomy, some authors have called into question the necessity of this procedure in most circumstances [3].

Surgical Approach to Specific Causes of Multiglandular Parathyroid Disease

Sporadic Primary Hyperparathyroidism

Primary hyperparathyroidism is relatively common, with an estimated incidence of up to 2.1 % in postmenopausal females [4]. Most of these cases are relatively mild and may be managed medically; only a small percentage of patients require surgical intervention [5]. Symptomatic hyperparathyroidism (nephrolithiasis or symptomatic hypercalcemia) should undergo surgery. The vast majority of patients are asymptomatic; in these patients, current guidelines recommend parathyroidectomy for serum calcium levels 1.0 mg/dl or more above the upper limit of normal, estimated glomerular filtration rate <60 ml/min, bone density at the hip, distal radius, or lumbar spine >2.5 standard deviations below peak bone mass (T score <−2.5), 24 h urine calcium >400 mg/day, nephrolithiasis on radiograph, ultrasound, or CT, or patient age <50 years [6]. In sporadic primary hyperparathyroidism, multiglandular disease occurs in 10–15 % of patients. Multiglandular disease more often manifests as mild hypercalcemia; severe hypercalcemia is usually due to an adenoma [7]. Multiglandular disease is often encountered in younger male patients with nephrolithiasis despite only mildly elevated serum calcium [8]. Thus, patients with only mild elevations in serum calcium but who are otherwise indicated for surgery should be approached with caution, and are likely best treated by those with specialized experience.

The underlying cause of sporadic hyperparathyroidism remains unknown, although some inroads have been made in understanding the molecular pathology of this disease. Alterations in cyclin D1, a regulator of the retinoblastoma protein and cell cycle control, were the first described mutations associated with hyperparathyroidism [9]. Sporadic mutations in the MET-1 gene have also been implicated in the development of this disease [10]. The presence of certain polymorphisms in the vitamin D receptor has been linked to mild primary hyperparathyroidism [11]. However, whole exome sequencing of hyperplastic parathyroid glands showed a wide heterogeneity in mutations present, suggesting a more complex, multifactorial pathogenesis for this disease [10]. Histologically, the parathyroid glands in patients with multiglandular disease demonstrate nodular chief cell hyperplasia. This is typically not symmetric among glands; usually only two or three glands are enlarged, and these nodules appear similar to small adenomas. In fact, these glands are often indistinguishable from multiple adenomas [12]. In most patients with multiglandular disease, two glands are enlarged; cases with three or four enlarged glands are more uncommon [7, 13]. Obvious four gland enlargement is more likely to represent water clear cell hyperplasia or patients with unrecognized MEN1 syndrome.

Preoperative imaging with ultrasound, 4-D CT, and/or sestamibi scanning is very useful in detecting adenomas but is typically not sensitive enough to adequately detect multiglandular disease. Thus, in the absence of clear localizing studies, the surgeon must be prepared for exploration of all four parathyroid glands. Generally in cases of multiglandular sporadic hyperparathyroidism, only the enlarged glands are excised, and the normal-appearing glands are left intact [14]. In patients with double adenomas, two glands are excised; in those with three or four enlarged glands, subtotal parathyroidectomy is recommended [15]. A cervical thymectomy should also be considered when multiple abnormal glands are seen, as supernumerary glands are often found within the thymus. Water-clear cell hyperplasia may be discovered during the procedure; this manifests as four gland disease with exceptionally enlarged, brownish parathyroid glands. In these cases the parathyroid tissue does

not function well, thus a much larger remnant should be preserved after subtotal parathyroidectomy [16].

Lithium-Induced Hyperparathyroidism

Lithium therapy is a common treatment for bipolar disease, and patients are often on this medication for many years. Lithium may cause hypercalcemia due to hyperparathyroidism in 5–50 % of patients [17, 18]. The exact mechanism by which this occurs remains unclear; lithium appears to antagonize the calcium receptor in parathyroid cells, thereby reducing calcium-induced PTH suppression, or it may directly stimulate PTH release from the parathyroid cell [19]. Hypercalcemia typically develops after many years of lithium treatment, and is characterized by mild hypercalcemia with only moderately elevated PTH levels. In a small subset of patients, hypercalcemia may develop rapidly after the initiation of lithium therapy. This is typically due to unrecognized primary hyperparathyroidism unmasked by lithium therapy; generally an adenoma may be identified in these patients and cured with surgery.

Withdrawal from lithium therapy will often correct hypercalcemia; however, not all patients are able to discontinue therapy. While medical management is possible, in the long term surgery is often more efficacious and cost effective. Multiglandular disease is more common than in sporadic hyperparathyroidism, with rates ranging from 25 to 56 % [20–23]. Because of this fact, a four-gland exploration has been the gold standard for surgical treatment for many years. Excision of any abnormally-sized gland with preservation of normal appearing glands is typically sufficient for cure. With advances in preoperative localization and intraoperative PTH (IOPTH) assays, many are now moving to minimally invasive parathyroidectomy in those patients where a single abnormal gland can be localized [24]. However, standard criteria for a postoperative decrease in IOPTH level to <50 % of baseline do not always adequately predict cure in these patients [21, 23]. False positive IOPTH result occurs when IOPTH reduces more than 50 % from pre-excision level however another remaining enlarged gland can subsequently hypersecrete. Long-term cure rates with surgery generally exceed 80 % [22].

Parathyromatosis

Parathyromatosis is a rare cause of recurrent or persistent hyperparathyroidism and is exceeding difficult to manage. It consists of numerous islands of hyperfunctioning parathyroid tissue scattered throughout the neck and mediastinum. Two etiologies have been proposed for this: either intraoperative spillage and seeding of parathyroid tissue throughout the operative field during parathyroidectomy or hyperplasia of preexisting embryological rests of parathyroid tissue. Although a few early reports of scattered hyperfunctioning parathyroid tissue at primary surgery exist to support the latter theory of pathogenesis, most surgeons believe that parathyromatosis is due to intraoperative spillage during parathyroidectomy [25, 26]. Occasionally parathyromatosis may be diagnosed on localization studies such as ultrasound [27, 28], but it is more commonly discovered intraoperatively. Surgical management of this condition is usually unsuccessful; it is often difficult to identify all nodules of parathyromatosis, and these nodules are typically adherent to old surgical scar or other structures making excision difficult. If discovered during surgery, removal of obvious parathyromatosis or a formal unilateral level VI dissection for unilateral disease may be attempted, but medical management will often be required over the long term.

Multiple Endocrine Neoplasia Type I

MEN-1 is a relatively rare autosomal dominant disease affecting approximately 1 in 30,000 people [29]. This syndrome is manifested by tumors of the pancreas (neuroendocrine pancreatic tumors), pituitary, and parathyroid glands. Other tumors associated with MEN-1 include lipomas,

carcinoid tumors, facial angiofibromas, pheochromocytomas, thyroid neoplasms, and adrenocortical adenomas [30]. MEN-1 is caused by mutations in the *MEN-1* gene on chromosome 11q13 [31, 32]. This gene encodes the menin protein, which is involved in regulation of transcriptional regulation, although its exact function remains unknown. It is believed to function as a tumor suppressor and leads to tumor formation via the "two-hit" hypothesis: patients with MEN-1 possess a germline mutation in one of the two copies of *MEN1*; when a random mutation occurs in the second copy in a cell, this initiates clonal expansion and tumor formation.

More than 1000 germline *MEN1* mutations have been identified, which account for 70–90 % of families with MEN-1 [29, 33, 34]. Unlike MEN-2A, this large number of mutations has prevented the development of clear genotype-phenotype correlations; at this point mutational analysis cannot predict tumor distribution, disease severity, or age of onset [30]. Despite this, families may demonstrate relatively consistent disease phenotypes. Thus, genetic testing remains useful in order to follow patients prospectively for close testing, or to rule out disease in subjects within families with known mutations. However, negative genetic testing does not exclude the disease in potential probands, as even full *MEN1* gene sequencing detects only 70–90 % of mutations in patients with classic MEN-1 features [35].

Current guidelines recommend testing for MEN1 mutations in several situations: an index case with two or more MEN-1-associated endocrine tumors, first degree relatives of *MEN1* mutation carriers, or in patients with possible atypical MEN-1, development of a single MEN-1-associated tumor such as islet cell tumors, gastrinoma, or multiglandular parathyroid disease at a young age, or two or more MEN-1-associated tumors not part of the classic triad (pancreas, pituitary, parathyroid) [36]. Testing for *MEN1* mutations in first-degree relatives of known *MEN1* carriers is particularly important, as it will indicate those individuals that should be screened closely for MEN-1-associated tumors and those that do not need extensive testing and may be relieved of the anxiety of possible tumor development. When possible, testing should occur in children before 10 years of age, as MEN-1 tumors have been reported in children as young as 10 [37]. See the chapter "Familial hypocalcuric hypercalcemia (FHH) genetic testing and counseling for hyperparathyroidism" for more information.

Primary hyperparathyroidism is the most common feature of MEN-1 and occurs in up to 90 % of patients [38]. MEN-1-associated hyperparathyroidism accounts for approximately 2–4 % of all cases of primary hyperparathyroidism, and is characterized by a particularly aggressive multiglandular disease [38, 39]. Given the "two-hit" hypothesis regarding the pathogenesis of MEN-1, the parathyroid disease in this condition is typically asymmetric and multiglandular. As the "second hit" is unlikely to occur synchronously in two parathyroid glands, gland enlargement occurs at different times. Normal appearing parathyroid glands are not uncommonly reported in MEN-1 patients, although the frequency of finding normal glands decreases with age, and the "second hit" is highly likely to occur over time [33, 40]. Onset of hyperparathyroidism in MEN-1 patient is usually much earlier than in patients with sporadic hyperparathyroidism, typically in the third or fourth decade; by age 50 virtually all MEN-1 patients will develop hyperparathyroidism [38, 40]. The degree of bone mineral loss in hyperparathyroidism patients is also typically more severe than in patients with sporadic hyperparathyroidism.

Patients with known *MEN1* mutations should undergo yearly screening for parathyroid disease with measurement of serum calcium and parathyroid hormone levels [37]. Once detected, localization studies such as ultrasound and sestamibi are not particularly useful, as all glands are usually affected and a bilateral neck exploration is needed. However, if an ectopic gland is suspected, preoperative imaging may be useful to guide the exploration. The indications for parathyroidectomy in MEN-1 are no different than for patients with sporadic hyperparathyroidism: symptomatic patients should undergo surgery, while asymptomatic patients may undergo surgery based on previously discussed guidelines.

However, given the progressive and aggressive nature of parathyroid disease, the timing of surgery should carefully consider surgeon experience, patient preferences, and availability of long-term calcium monitoring facilities prior to undertaking surgery in asymptomatic patients. Given the high likelihood of future revision surgery, particularly in young MEN-1 patients, it has been suggested to reserve surgery for patients with symptomatic hyperparathyroidism, and carefully monitor asymptomatic patients for symptoms and complications [37]. Calcimimetics may be used in patients where surgery is contraindicated, or has failed to cure the hyperparathyroidism [41].

Given the progressive nature on hyperparathyroidism in MEN-1, permanent cure of hyperparathyroidism is typically not possible. Thus, the aim of surgery should be to minimize the risk of permanent hypoparathyroidism while providing the longest possible recurrence-free interval. In the past, parathyroidectomy removing only the enlarged glands and leaving one or more intact parathyroid glands has been attempted for MEN-1 patients. This approach was found to lead to unacceptably high rates of recurrence, ranging from 23 to 61 % in various studies [42–44]. When compared to subtotal or total parathyroidectomy, patients undergoing less than subtotal parathyroidectomy had a significantly shorter median recurrence-free survival (7 vs. 16.5 years) and a substantially lower rate of 10-year recurrence free survival (37 % vs. 61 %) [45]. Thus, this approach has largely been abandoned for either subtotal parathyroidectomy or total parathyroidectomy with autotransplantation.

In most MEN-1 patients undergoing initial surgery, subtotal parathyroidectomy is the preferred operation. The recurrence rates of hyperparathyroidism in studies of this procedure are generally dependent on the length of follow up; as all parathyroid tissue in these patients harbors the *MEN1* mutation, any residual parathyroid tissue is likely to become hyperplastic if given sufficient time. In fact, in one study the length of follow up time was one of the best predictors of recurrence in multivariate analysis [46]. Recurrence rates after subtotal parathyroidectomy have been reported between 13 and 35 % after several years of follow up [45–47]. Comparison of this technique with less than subtotal parathyroidectomy and total parathyroidectomy have shown the rate of recurrence is significantly better than procedures removing less than a subtotal parathyroidectomy, but somewhat increased from total parathyroidectomy. However, the rate of severe hypocalcemia is significantly increased with total parathyroidectomy, (46 % vs. 26 % with subtotal parathyroidectomy) requiring chronic calcium supplementation and careful serum calcium monitoring [45]. Thus, in order to minimize harm to patients, a subtotal parathyroidectomy has become the procedure of choice during initial surgery for MEN-1 hyperparathyroidism.

Bilateral neck exploration is required, and all four parathyroid glands are identified. The most normal-appearing gland of the four should be selected to remain in the body, ideally leaving equivalent of a normal size gland (approximately 40–50 mg of tissue or less, or less than double the size of a normal gland). If partial resection of a gland is needed, a hemoclip should be placed across the gland and sharp division performed just distal to this clip; this will both help to prevent seeding of hyperplastic parathyroid cells into the nearby tissues and also facilitate localization of the gland if reoperation is needed. Once this has been performed and the parathyroid remnant appears well-vascularized, the remaining three abnormal parathyroid glands are resected. A cervical thymectomy should also be performed during this procedure, as there is a high incidence of ectopic parathyroid glands or tissue that may lead to future recurrence. Up to 30 % of MEN-1 patients have ectopic or supranumerary parathyroid glands, and the removal of the thymus may identify up to 50 % of these ectopic glands [48] . Preoperative imaging with CT imaging and/or Sestamibi is also useful to identify any ectopic glands. Once all other parathyroid glands have been resected, an intraoperative parathyroid hormone level may be obtained; if the parathyroid hormone level becomes undetectable, autotransplantation of parathyroid tissue into the nondominant forearm may be considered; however, this is not routinely required.

While total parathyroidectomy may not be routinely utilized as the initial procedure for MEN-1, there are situations where it is the preferred procedure. In patients with four markedly enlarged parathyroid glands, this procedure obviates the need to trim a diseased parathyroid within the neck, with associated risk of later parathyromatosis. This is also the preferred procedure during revision surgery, as further surgeries in the neck are likely to be complicated by scarring and adhesions. Total parathyroidectomy involves removal of all four parathyroid glands from the neck. The most normal-appearing gland is then selected for autotransplantation. Approximately 60–80 mg of tissue is minced and then placed into small pockets within the muscle of the nondominant forearm. Thus, recurrent disease within the forearm can be treated with excision of the parathyroid autograft under local anesthesia, obviating the need for general anesthesia for revision cervical surgery. The site of the autografts should be marked with hemoclips (Figure 1), and information regarding the number of clips as well as their precise anatomic location should be dictated in the operative note to facilitate excision of the autograft.

Reported results of total parathyroidectomy are often quite good, with many authors demonstrating zero recurrences within the neck [49]. As discussed previously, overall recurrence rates are also somewhat better than those seen after subtotal parathyroidectomy. However, the major drawback to this procedure is the high likelihood of severe and persistent hypocalcemia after surgery. While the autografts typically functional in approximately 4 weeks, the rate of functional return is variable. In one series, up to 40 % of autografts remained nonfunctional nearly 3 years after surgery, requiring prolonged hypocalcemia treatment and monitoring [50]. Other authors have reported somewhat better results, although a hypocalcemia remained a significant problem in a number of patients [45, 47]. Given these risks, this procedure is typically reserved for recurrent or particularly problematic cases of MEN-1-associated hyperparathyroidism.

Multiple Endocrine Neoplasia 2A

MEN-2A is an autosomal dominant disorder characterized by medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism. Medullary thyroid cancer occurs in 70–100 % of MEN-2A patients; pheochromocytomas occurs in about 50 % of patients, and hyperparathyroidism is seen in 20–30 % of patients [51]. Other uncommon manifestations of this syndrome include Hirshprung's disease and cutaneous lichen amyloidosis. MEN-2A is caused by mutations in the RET protooncogene, and occurs in approximately 1 in 30,000 people [39]. Over 50 different point mutations have been identified in the RET gene, and current genetic tests can detect nearly 100 % of mutation carriers [52]. There is a strong correlation between individual RET mutations and disease phenotype, including age of onset, medullary thyroid carcinoma aggressiveness, and the presence of other endocrine abnormalities.

Based on genotype-phenotype associations, the American Thyroid Association created a risk stratification system based on the genetic mutation present and its correlation to the risk and aggressiveness of medullary thyroid carcinoma, with specific diagnostic and treatment recommendations based on this risk stratification [53]. While this risk stratification is primarily concerned with medullary thyroid carcinoma, genotype correlations to hyperparathyroidism are also well established. Primary hyperparathyroidism is most common in patients with the C634R mutation, although it is less commonly seen in several other genotypes, including E768D, S649L, L790F, Y791F, V804L, V804M, S891A, C609F/R/G/S/Y C630R/F/S/Y, and others [52]. Thus, knowledge of a patient's specific mutation may alter long-term screening for hyperparathyroidism and the approach to initial thyroidectomy.

Hyperparathyroidism in MEN-2A is generally mild, with only slight elevation of serum calcium and infrequent symptoms [39, 54]. The median age of onset is around 38 years; current guidelines recommend that yearly screening with serum calcium and PTH measurements begin at 8 years of age in patients with C634R and C630R/

F/S/Y mutations, and by age 20 in all other MEN-2A patients [53]. Similar to other familial forms of hyperparathyroidism, MEN-2A-associated hyperparathyroidism is generally considered to be multiglandular; however, adenomas and asymmetric gland enlargement are much more common than in MEN-1. In one study, 43 % of MEN-2A patients had a single adenoma and 45 % had multiglandular hyperplasia [55]. Ectopic or supernumerary glands may be present, but are not as common as in MEN-1.

The indications for parathyroidectomy in MEN-2A are the same as in sporadic hyperparathyroidism or MEN-1. However, given the prevalence of medullary thyroid carcinoma, most patients with MEN-2A undergo total thyroidectomy, often at a young age, along with possible central compartment dissection. The high likelihood of previous neck surgery in MEN-2A patients therefore makes parathyroidectomy much more difficult. In the occasional patient that has not had prior surgery, or where hyperparathyroidism is discovered prior to a planned thyroidectomy, a four-gland exploration is recommended at the time of thyroidectomy. Given the much higher incidence of single or double adenoma and the milder course of MEN-2A-associated hyperparathyroidism, the primary focus of surgery should be preservation of parathyroid function, with removal of only grossly abnormal glands. The location of other parathyroid glands may be marked with surgical clips, as these may be useful in case later reoperation is necessary.

In patients that have had previous thyroidectomy, the previous operative records should be carefully reviewed to determine which parathyroid glands were identified and/or removed at surgery, to avoid unnecessary dissection. Given the difficulty of parathyroid exploration in a previously dissected thyroidectomy bed, preoperative localization studies should be utilized, and a more directed surgical approach for only those glands found to be grossly abnormal on imaging may be employed. Four-dimensional CT scans have been shown to be superior to both ultrasound and sestamibi scans in localizing abnormal glands, particularly in the reoperative setting [56].

Prior to any planned surgery, all MEN-2A patients should undergo screening for pheochromocytoma with either 24-h urinary metanephrine and normetanephrine, or plasma-free metanephrine and normetanephrine. If a pheochromocytoma is discovered, adrenalectomy should be performed prior to parathyroidectomy. However, this may occur immediately afterwards during the same anesthetic [53].

Familial Isolated Hyperparathyroidism

Familial isolated hyperparathyroidism consists of inherited hyperparathyroidism without other endocrine disorders. This is typically multiglandular disease, and mutations in the *MEN1* and *HRPT2* gene have been linked to this condition [57]. As such, many of these patients may be considered to have MEN-1 without expression of other endocrinopathies [58]. Surgical management of these patients is similar to those with MEN-1, where subtotal parathyroidectomy is the preferred primary surgery.

Hyperparathyroid Jaw Tumor Syndrome

Hyperparathyroid jaw tumor syndrome (HPT-JT) is a rare cause to familial hyperparathyroidism, often occurring in younger patients. In addition to hyperparathyroidism (either single or multiple adenomas), patients also have an increased risk of parathyroid carcinoma, ossifying jaw fibromas, renal abnormalities, and uterine tumors [59, 60]. In HPT-JT syndrome, parathyroid carcinoma may occur in up to 15 % of patients, and jaw fibromas occur in about 35 %. HPT-JT has been associated with mutations of the *HRPT2* gene, which encodes parafibromin [59, 61]. Only about 50 % of families have detectible *HRPT2* mutations (epigenetic silencing may account for other instances of the disease), making genetic testing difficult [61]. Given the increased risk of parathyroid carcinoma in these patients, preoperative diagnosis and thorough evaluation is needed.

Parathyroid carcinoma should be suspected in any patients with markedly elevated parathyroid hormone levels (3–10× the upper limit of normal), serum calcium exceeding 14 mg/dl, or evidence of local invasion on preoperative imaging [62]. Fine needle aspiration is typically not recommended due to the difficulty in diagnosis and the risk of tumor rupture and parathyromatosis, thus diagnosis is typically made at surgery based on clinical suspicion and intraoperative pathology consultation [62].

Surgical indications for HPT-JT are identical to those for patients with MEN-1. This disease is typically managed with excision of only grossly enlarged glands, as single adenomas are more common in this syndrome than in MEN-1. However, in patients with parathyroid carcinoma, more extensive surgery is required, including resection of the diseased gland, ipsilateral thyroidectomy, wide local excision of surrounding soft tissue, and ipsilateral paratracheal lymph node dissection. More information can be found in the parathyroid carcinoma chapter.

Familial Hypocalciuric Hypercalcemia

Although not an actual cause of multiglandular parathyroid disease, familial hypocalciuric hypercalcemia (FHH), an inherited disorder caused by mutations in the calcium sensing receptor gene [63], may closely mimic primary hyperthyroidism; therefore it is critically important for the parathyroid surgeon to understand this entity. The end result of this mutation is alterations in calcium sensing in the parathyroid glands and increased calcium reabsorption in the kidney. Patients with FHH generally demonstrate increased parathyroid hormone levels and serum calcium values that closely resemble that seen in patients with primary hyperparathyroidism. However, unlike primary hyperparathyroidism, this is a completely benign condition with little to no long-term consequences for patients. Life expectancy is probably normal, although the there is some question whether the mild parathyroid hyperplasia seen in some FHH patients may predispose them to the development of hyperparathyroidism [64]. The main impetus for correctly diagnosing a patient with FHH is to avoid an unnecessary and futile parathyroidectomy. FHH should be suspected in patients with asymptomatic hypercalcemia, either with or without elevated parathyroid hormone levels, in patients with hypocalciuria, in patients with family members with asymptomatic hypercalcemia or previous unsuccessful parathyroidectomy, or in patients with recurrent hypercalcemia after parathyroidectomy with either normal histology or mild hyperplasia. The primary screening test for FHH is measurement of the calcium/creatinine clearance ratio with a 24-h urine collection; A calcium/creatinine clearance ratio <0.020 will exclude two thirds of patients with primary hyperparathyroidism, while >98 % of FHH patients will fall below this level. In patients with a low calcium/creatinine clearance ratio, genetic testing for *CASR* gene mutations is then performed to confirm the diagnosis of FHH [65]. A 24 h urine calcium collection is recommended for all patients with likely asymptomatic hyperparathyroidism in order to avoid unnecessary surgery on patients with FHH.

Secondary/Tertiary Hyperparathyroidism

Secondary hyperparathyroidism refers to elevated parathyroid hormone levels in response to a physiological stimulus, i.e. low serum calcium levels. The most common causes of secondary hyperparathyroidism are vitamin D deficiency and chronic kidney disease. While vitamin D deficiency is typically easily correctible, hyperparathyroidism due to chronic kidney disease does occasionally require parathyroidectomy. Surgery will be required in about 10 % of patients on dialysis for over 10 years, and almost 30 % of patients on dialysis for greater than 20 years. In some patients that undergo renal transplantation, elevated parathyroid hormone levels may persist despite normalization of renal function; this entity is known as tertiary hyperparathyroidism.

Chronic renal disease induces hyperparathyroidism due to multiple metabolic abnormalities,

including hypocalcemia, hyperphosphatemia, and abnormal vitamin D metabolism. Hyperphosphatemia is a primary driver of pathogenesis; it acts directly on parathyroid cells to induce parathyroid hormone secretion and cellular proliferation [66]. The effects of hyperphosphatemia are mediated by the action of FGF23, a growth factor produced by osteocytes in response to phosphate retention, and this protein directly stimulates proliferation and hormone secretion from the parathyroid glands and inhibits vitamin D activation [67, 68]. These metabolic changes and persistent hyperparathyroidism lead to increased bone turnover and osteitis fibrosa cystica; ultimately the bone becomes fibrotic and weak, and patients may experience pathologic fractures and skeletal deformities.

Ectopic calcification is also a significant concern and may result in calcifications of the subcutaneous tissue, lungs, heart valves, muscles, joints, and vascular system. These changes may lead to significant cardiovascular disease and other problems that are a significant cause of mortality in chronic renal disease [69]. Calciphylaxis is a rare but dreaded complication of secondary hyperparathyroidism, characterized by progressive calcification of the media of vessels Refer to the calciphylaxis chapter. This leads to ischemia and tissue necrosis, gangrene, and sepsis. The mortality rate of this condition is nearly 50 %. While medical intervention is typically used to lower serum calcium and phosphorus levels as quickly as possible, urgent parathyroidectomy is typically required if elevated parathyroid hormone levels accompany calciphylaxis [70].

Secondary hyperparathyroidism typically leads to asymmetric enlargement of the parathyroid glands, often with nodularity present. Chronic renal disease has been hypothesized to initially provoke diffuse enlargement of the glands; unknown genetic mutations within the glands then trigger the development of nodules, which may eventually develop into large, dominant nodules unresponsive to calcium levels [71, 72]. Under expression of the vitamin D receptor and the calcium sensing receptor has been described in parathyroid tissue from patients with chronic renal disease [73, 74], suggesting that medical therapy may be less effective in these patients.

Given the risk for significant morbidity and mortality from secondary hyperparathyroidism, the United States Kidney Foundation has proposed guidelines for management of this disease through the Kidney Disease Outcomes Quality Initiative [75]. The guidelines recommend that patients undergoing hemodialysis should have serum calcium levels restricted to 8.4–9.5 mg/dl, serum phosphorus levels between 3.5 and 5.5 mg/dl, and parathyroid hormone levels between 150 and 300 pg/ml. Most patients are able to be managed with medical therapy, which may include phosphate binders, phosphate restriction, vitamin D receptor activators, and calcimimetics. Adequate and frequent hemodialysis is also useful to control phosphate and calcium levels. An emphasis is placed on prolonging patient survival rather than avoidance of bone abnormalities.

Parathyroidectomy is recommended in cases of severe persistent hyperparathyroidism (serum parathyroid hormone >800 pg/ml) associated with hypercalcemia and/or hyperphosphatemia that is unresponsive to medical therapy [75]. The Japanese Society for Dialysis Therapy has published separate guidelines that suggest intervention earlier in the progression of disease; these recommend parathyroidectomy for serum parathyroid hormone levels >500 pg/ml with associated hyperphosphatemia and hypercalcemia unresponsive to medical therapy [76]. Furthermore, parathyroidectomy is indicated in patients with any clinical manifestations such as bone or joint pain, muscle weakness, bone loss, persistent anemia unresponsive to erythropoetin, progressive ectopic calcifications, dilated cardiomyopathy, or calciphylaxis. Ultrasound assessment of the parathyroid glands is also recommended, as glands with a volume >500 mm^3 or largest diameter >1 cm are likely to harbor nodular hyperplasia and demonstrate resistance to medical therapy.

Secondary hyperparathyroidism affects all parathyroid glands, thus surgical intervention should address all glands, including potential ectopic or supernumerary glands. Subtotal parathyroidectomy is appropriate in patients with a planned renal transplantation in the near future or if a grossly normal appearing parathyroid gland

is identified during exploration. However, in many cases all four glands will appear markedly abnormal, thus a total parathyroidectomy with autotransplantation should be performed. A randomized trial of patients with secondary hyperparthyroidism showed no difference in recurrence rates between subtotal parathyroidectomy and total thyroidectomy with autotransplantation [77], and a recent meta-analysis also concluded that both procedures are equally effective [78]. However, many surgeon feel that total parathyroidectomy with autotransplantation is the optimal treatment due to the ease of reoperation for recurrent disease in these challenging and often medically frail patients.

In long-term dialysis patients, autotransplantation after total parathyroidectomy may be performed, but is not always necessary. Some parathyroid hormone production is often observed after total parathyroidectomy due to additional nests of ectopic parathyroid tissue within the thymus [79, 80], and frequent dialysis along with vitamin D and calcium supplementation is often sufficient to maintain calcium and bone homeostasis in these patients. While avoidance of autotransplantation is not recommended in patients that may be candidates for renal transplantation due to the difficulty in controlling calcium levels after transplantation [75, 76], it is a viable option in those patients that are not transplant candidates. Total parathyroidectomy without autografting may provide lower recurrence rates than when autotransplantation is performed, and hypocalcium can be managed exogenously by increasing the concentration of calcium in the dialysate [79–82].

Alternative procedures to ablate parathyroid tissue, including percutaneous ethanol injection (PEIT), radiofrequency ablation, and high-intensity focused ultrasound have been utilized in patients with secondary hyperparathyroidism [83, 84]. PEIT is most efficacious in patient with a single enlarged gland >500 mm^3 in volume [85]. However, PEIT makes subsequent identification of parathyroid tissue and the recurrent laryngeal nerve during surgery extremely difficult [86]. Thus, PEIT is best utilized in patients with only a single enlarged gland, those that have undergone previous subtotal parathyroidectomy, or those who cannot tolerate general anesthesia for parathyroidectomy due to medical comorbidities.

Tertiary hyperparathyroidism refers to the persistence of chronic renal disease- induced hyperparathyroidism following renal transplantation. Following renal transplantation, most patients exhibit elevated parathyroid hormone, hypercalcemia, and hypophosphatemia. In the majority of patients, hypercalcemia and hypophosphatemia resolve within 1 year, and further intervention is not needed. However, somewhere between 1 and 5 % of renal transplant patient will require surgical intervention. Cinacalcet has been shown to have some efficacy in the treatment of tertiary hyperparathyroidism [87], although parathyroidectomy may be a better long-term solution [88].

Indications for surgery in tertiary hyperparathyroidism include persistent hypercalcemia greater than 6 months after transplant, low bone mineral density, deterioration of renal graft function due to hyperparathyroidism, nephrolithiasis, and symptomatic hyperparathyroidism. Both subtotal parathyroidectomy and total parathyroidectomy with autograft may be utilized in the treatment of tertiary hyperparathyroidism [89]. Many patients may have apparent one- or two-gland disease based on preoperative localization studies. However, as this disease is caused by initial hyperplasia of all four glands followed by autonomous hyperfunction of one or more glands subsequent to renal transplantation, asymmetric hyperplasia or incomplete resolution of all hyperplastic glands occur in up to 30 % of patients. Therefore, procedures less than bilateral exploration and subtotal parathyroidectomy have a high failure rate [90].

Decreased renal graft function is a concern following parathyroidectomy, which may be a result of transient hypoparathyroidism following parathyroidectomy. There is some evidence that subtotal parathyroidectomy may preserve renal graft function better than total parathyroidectomy with autografting [89], thus most surgeons advocate for subtotal parathyroidectomy rather than total parathyroidectomy. In one study of 105 tertiary hyperparathyroidism patients undergoing subtotal parathyroidectomy, hypercalce-

mia resolved in 97 % of patients, although over 20 % had some persistent hyperparathyroidism at 2 years follow up [91]. Glomerular filtration rate dropped by less than 10 % after 1 year, and there was no mortality observed, thus this surgery appears quite effective and safe in tertiary hyperparathyroidism patients.

Summary

Multiglandular parathyroid disease is relatively common, and accounts for approximately 10 % of cases of sporadic hyperparathyroidism. Thus, parathyroid surgeons should be comfortable with full parathyroid exploration and potentially prepared for at least a unilateral exploration regardless of the results of preoperative localization studies. Numerous other diseases and syndromes may lead to multiglandular hyperparathyroidism, and the surgical approach to these must be tailored to the unique pathophysiology and long-term prognosis of the specific cause of hyperparathyroidism.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion

Surgical management of multiglandular disease is challenging and different for primary, secondary, and tertiary hyperparathyroidism. The most important principle is to avoid the dreaded complication of permanent hypoparathyroidism. The surgeon should treat every parathyroid gland as possibly the last one the patient may be left with. When performing subtotal parathyroidectomy, resist the temptation to completely excise an enlarged parathyroid gland as it is initially and do so after determining that a portion of one of the glands can be left that will be viable. Every parathyroid gland should be handled with utmost care, preserving its blood supply.

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Intraoperative PTH Monitoring for Parathyroid Surgery

22

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Contents

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Introduction

Intraoperative parathyroid hormone (PTH) monitoring is now a commonly utilized tool in the surgical management of patients with primary hyperparathyroidism (pHPT). Recently, intraoperative PTH monitoring has become standard of care for many centers specializing in parathyroid surgery. Its use during parathyroidectomy guides the surgeon in operative decision making, helps to avoid unnecessary bilateral neck dissection, and is an often critical aspect of the surgery itself [1].

Historically, the operative approach to patients with sporadic pHPT included bilateral neck exploration with identification of all parathyroid glands and excision of those glands thought to be enlarged and therefore potentially abnormal. This operative method, often considered the gold standard for multi-gland parathyroid disease, is highly subject to the surgeon's judgment and therefore difficult to standardize. Technological advances, including new techniques in nuclear medicine, have led to improved localization of

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abnormal parathyroid glands prior to surgery. Advances in preoperative imaging, along with intraoperative PTH monitoring, have allowed endocrine surgeons the ability to perform less invasive and focused parathyroid surgery [1].

The goals of this chapter are to discuss the role of intraoperative PTH monitoring during parathyroid surgery, its technical aspects, and indications. Furthermore, we discuss the use of intraoperative PTH monitoring as a guide for predicting operative success among patients with pHPT.

History of Intraoperative PTH Monitoring

Both the discovery of parathyroid hormone and its use as a method to identify hypersecreting parathyroid tissue provided the basic premise for intraoperative PTH monitoring. Over the course of decades, several important discoveries paved the way for PTH assays to become quick, easy, and useful in real-time intraoperative settings. These discoveries provided the foundation for the current application of intraoperative PTH monitoring in managing parathyroid disease.

Parathyroid hormone was first identified in 1923 when a general surgeon, A.M. Hanson, used the bovine hormone extract to treat tetany [2]. Years later, researchers were able to isolate the hormone and demonstrate its relationship with the hypercalcemic properties described by A.M. Hanson. In the 1960s, researchers collaborating with the National Institute of Health described a radioimmunoassay for the detection of PTH [3]. This was further elucidated by Nussbaum in the 1980s. Nussbaum noticed a rapid decline of PTH levels within hours following the successful excision of parathyroid adenomas in patients with pHPT [4]. In 1988, he and his colleagues published a study describing their experience using a sensitive immunoradiometric assay for documenting decline of the biologically active, intact PTH molecule to less than 40 % of baseline PTH values 15 min after successful parathyroid adenoidectomy [4]. George Irvin from the University of Miami was one of the first advocates in the USA for the use of intraoperative PTH monitoring to guide parathyroidectomy. In 1991, Dr. Irvin published his experience using a modified real-time PTH "quick" test that predicted postoperative calcium levels [5].

A variety of immunoassays were soon developed to assist in the diagnosis of hyperparathyroidism [6]. When the advantages of immunochemiluminescence over immunoradioisotopic methods for PTH measurement were demonstrated, a "rapid" PTH assay became widely available [7–9]. Most immunochemiluminescence assays use goat antibodies, either polyclonal or monoclonal, against specific PTH molecular segments [8]. The PTH molecule and antibodies form a "sandwich complex" with one antibody catalyzing a light-emitting reaction [8, 10]. The rate of light output is directly related to the amount of bound antibody and therefore proportional to the PTH level [10].

By 1996, PTH assays became commercially available for intraoperative PTH monitoring, with turnaround times ranging from 8 to 20 min [8, 10]. Over the next decade, intraoperative PTH monitoring became an essential tool for the surgical management of sporadic pHPT. Currently, over 90 % of high-volume endocrine surgeons utilize intraoperative PTH monitoring to guide parathyroidectomy in these patients [1].

Indications for Intraoperative PTH Monitoring During Parathyroidectomy

Intraoperative PTH monitoring guides the surgeon during parathyroidectomy in several instances. First, intraoperative PTH monitoring helps to confirm complete excision of all hyperfunctioning parathyroid glands without direct visualization of all normally functioning glands. Second, an insufficient PTH decline following removal of parathyroid tissue indicates additional hypersecreting parathyroid tissue and the need to further explore the neck to achieve operative success. Third, intraoperative PTH assays may provide biochemical confirmation of parathyroid versus non-parathyroid tissue on fine-needle aspirations [11]. A fourth application is to use

PTH assays from bilateral jugular venous sampling to determine the side of the neck with hypersecreting parathyroid tissue [8].

Ultimately, the most common use of intraoperative PTH monitoring is to allow the surgeon to perform a focused and minimally invasive parathyroidectomy for pHPT. There is some controversy over whether intraoperative PTH monitoring adds to the accuracy and speed of parathyroid surgery if preoperative localization studies are concordant or a normal ipsilateral parathyroid gland is visualized. A recent prospective two-institution trial addressed this question [12]. A total of 2162 patients from two institutions were included and the rate of persistent hypercalcemia, or operative failure, was 1.5 % among all patients. However, if the study population had undergone exploration dictated by preoperative localization studies or the appearance of the ipsilateral parathyroid gland, then the risk of persistent hypercalcemia would have increased by 8.7-fold [12]. The authors concluded that intraoperative PTH monitoring remains a useful tool for predicting operative success.

The use of intraoperative PTH monitoring has been extensively described in patients with sporadic pHPT. However, its use and indication in patients with secondary and tertiary hyperparathyroidism and multiple endocrine neoplasia (MEN) have been less robust [8, 13, 14]. Intraoperative PTH monitoring in patients with familial hyperparathyroidism undergoing parathyroidectomy has been demonstrated with accuracy [15]. For patients with parathyroid carcinoma, the use of intraoperative PTH monitoring to predict postoperative and long-term eucalcemia is controversial [16, 17].

Technique for Intraoperative PTH Monitoring

Blood Collection Access

After the patient is placed under general anesthesia, a peripheral intravenous line or an arterial line is obtained. A peripheral line in the foot is ideal as it is easily accessed by the anesthesia team throughout the course of surgery without compromising the sterile field. Once intravenous access is obtained, the anesthesia team should be instructed to discard the first 10 cc of blood with saline to avoid dilution of the remaining samples. Next, a 16-gauge catheter is placed and 3–5 cc of whole blood should be obtained prior to skin incision (pre-incision). Of note, hemolysis has been described to falsely decrease PTH levels and should be avoided [18].

Blood Collection Timing

Timing of peripheral blood sample collection throughout the procedure is controversial. For ease of convenience and cost, without compromising outcomes, many surgeons advocate a pre-incision PTH level and a 10–15 min post-excision PTH level to start. However, for some endocrine surgeons, multiple blood samples are obtained throughout the procedure at the following time points: (1) pre-incision; (2) when all blood supply to the suspicious gland is ligated (pre-excision or time zero); (3) 5 min post-excision; (4) 10 min post-excision; and (5) occasionally 20 min post-excision [8].

Intraoperative Criteria for Predicting Operative Success

Intraoperative PTH monitoring is a tool in the surgeon's armamentarium for performing successful parathyroid surgery. Therefore, it must be correctly interpreted and utilized by the endocrine surgeon in order to accurately predict the outcome. A widely accepted goal of parathyroid surgery is to render the patient eucalcemic for at least 6 months following surgery. Patients who undergo incomplete excision of hypersecreting parathyroid glands develop hypercalcemia and elevated PTH levels within 6 months following surgery. Recurrent hyperparathyroidism occurs in patients who develop hypercalcemia and hyperparathyroidism following at least a 6-month period of eucalcemia. This latter group does not represent surgical failure.

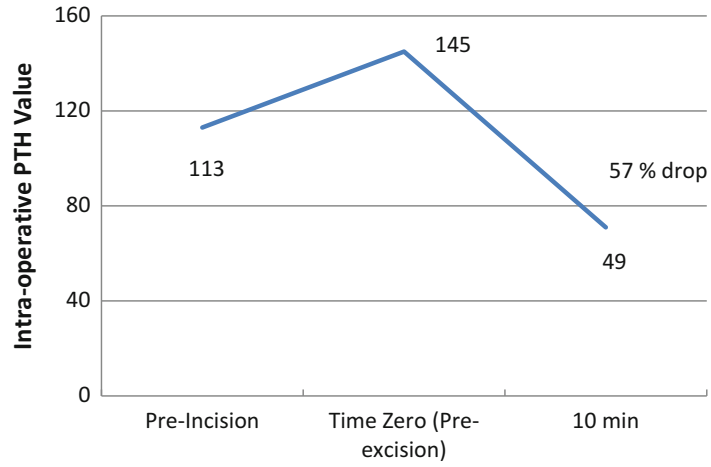

Fig. 22.1 Intraoperative PTH values at pre-incision, time zero (immediately prior to excision of parathyroid adenoma), and 10 min post-excision. There is a greater than 50 % PTH drop at 10 min post-excision compared to the pre-incision PTH value

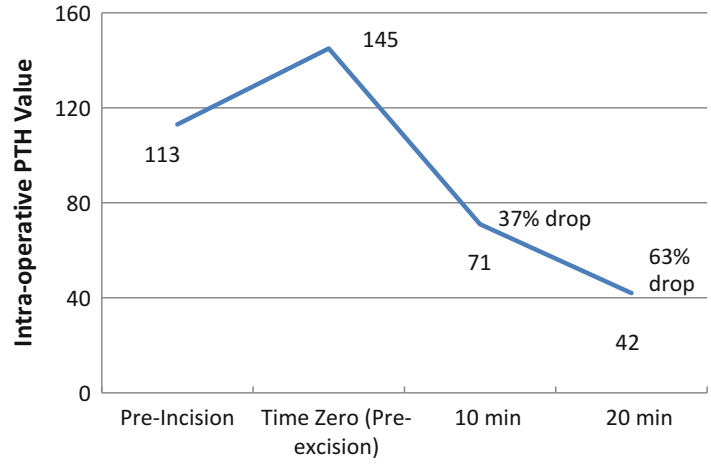

Fig. 22.2 Intraoperative PTH values at pre-incision, time zero, 10 and 20 min post-excision. There is only a 37 % drop in PTH at 10 min post-excision; therefore a 20-min post-excision PTH level is drawn which results in a greater than 50 % PTH drop

Most clinicians recommend using a greater than 50 % PTH drop criterion for measuring operative success [19]. In other words, the peripheral PTH level should drop more than 50 % from the pre-incision level (or the highest pre-excision value) at least 10 min after the removal of all abnormal parathyroid tissue and/or glands (Fig. 22.1). This criterion has been shown to predict postoperative normal or low calcium levels with 97–98 % accuracy [20–23]. If the 10-min post-excision PTH does not drop to within 50 % of the pre-excision value, then the neck must be re-explored for remaining hypersecreting parathyroid glands. If the post-excision PTH level drops but not by greater than 50 %, then a 20-min sample can be measured prior to re-exploration of the neck (Fig. 22.2). For each additional gland excised, a repeat PTH level is determined 10 min following each excision.

The "$>$50 % PTH drop" criterion is a reliable method for patients with sporadic pHPT. However, a modification has been proposed and utilized by some endocrine surgeons to improve the specificity of the assay [24]. The modification includes the following criteria: (1) a greater than 50 % PTH drop from the highest pre-excision value 10 min following gland excision and a PTH drop into the normal range *or* a $>$65 % PTH drop to predict operative success. If neither of these criteria are met after the 10-min post-excision PTH assay, then (2) a greater than 50 % PTH drop and a return to the normal range in 20 min are used as

the criterion for operative success. The accuracy, sensitivity, and specificity for this criterion are 97 %, 97 %, and 98 %, respectively [24]. Furthermore, this modification was reported to decrease false-positive results from 0.9 to 0.3 % without significantly increasing unnecessary neck exploration [8].

A retrospective review by Chiu and colleagues analyzed 352 patients who underwent parathyroidectomy for pHPT and correlated six different criteria for predicting operative success with actual 6-month postoperative PTH and calcium levels [25]. The investigators compared the following six criteria: (1) >50 % drop from the highest intraoperative PTH level at 10 min post-excision; (2) >50 % drop from the pre-incision PTH level at 10 min post-excision; (3) >50 % drop from the highest intraoperative PTH level at 10 min post-excision and a final PTH value within normal range; (4) >50 % drop from the highest intraoperative PTH level at 10 min post-excision and a final PTH value less than the pre-incision value; (5) >50 % drop from the highest intraoperative PTH level at 5 min post-excision; and (6) >50 % drop from the pre-excision PTH level at 10 min post-excision. After comparing each criterion with 6-month lab values, they found that satisfying criterion 3 had a high operative success rate but resulted in additional unnecessary neck exploration. Criterion 2 was better at predicting postoperative eucalcemia than criterion 3 [25].

Limitations in the Use of Intraoperative PTH Monitoring

Blood Sampling

Peripheral intravenous access is required for determining PTH levels both pre-incision and for at least one post-excision value. Many surgeons prefer to use the foot or arm for blood sampling. However, some prefer to collect samples from the internal jugular veins for ease of access. PTH values from the internal jugular veins are known to be higher absolute values than from a peripheral vein [26]. Although PTH levels will drop at a similar rate when compared to peripheral veins, they require a longer duration to reach the normal range. This complicates the scenario in which a surgeon relies on the 10-min post-excision PTH drop of >50 % *and* within normal range for operative success. The use of internal jugular veins from blood sampling therefore has the potential to increase unnecessary neck exploration or lead to longer operative times waiting for the PTH to drop to within normal range. In the case of a patient with very poor peripheral intravenous access, obtaining a blood sample from the jugular veins may be necessary. In these instances, it remains an accurate option for predicting postoperative calcium levels [26, 27].

Laboratory Error

Because operative success using intraoperative PTH monitoring is dependent on the PTH assay, errors in blood collection or laboratory processing can be devastating. The blood sample used for the PTH assay could be diluted or incorrectly measured either by the technician or an error in the system itself. It is crucial for the surgeon to understand the PTH assay technique and be able to evaluate the reported levels in the context of the clinical presentation intraoperatively. It is also important to confirm that the controls are within the expected reference range for that particular laboratory.

Delay in PTH Drop After Successful Parathyroid Adenoidectomy

After the excision of a hypersecreting parathyroid gland, occasionally the PTH does not drop enough to meet the surgeon's criteria for success. This more frequently occurs when the surgeon relies on a >50 % drop in PTH along with return to the normal reference range. In situations such as these, the authors recommend sending a 20-min post-excision PTH level in order to avoid further neck exploration. During difficult cases in which a significant amount of dissection is required for the identification of a parathyroid

adenoma, trauma to the gland and release of PTH are not uncommon. Therefore, during these instances, it may take longer for the PTH level to return to normal following excision.

Does Intraoperative PTH Predict Gland Size?

The use of intraoperative PTH monitoring guided by the ">50 % PTH drop" criterion has not been shown to predict macroscopic size of normally secreting parathyroid glands. The rate of multigland disease (MGD) is much lower when using intraoperative PTH monitoring to guide parathyroidectomy as opposed to gland size (3–10 % versus 13–28 %, respectively) [21, 23, 28–32]. In fact, when surgeons have used intraoperative PTH monitoring during bilateral neck exploration, they have demonstrated that 9–19 % of patients who met the criteria for operative success have another enlarged gland found on exploration [33]. Despite the finding of macroscopic glands on further exploration, there is no evidence that operative failure, or hypercalcemia occurring within 6 months post-procedure, occurs in these patients who met the ">50 % PTH drop" criterion [21, 23, 32, 34].

Miccoli and colleagues demonstrated the use of intraoperative PTH monitoring to guide surgery as opposed to morphologic gland size in a prospective randomized study of 40 patients. They demonstrated that patients who had bilateral neck exploration with parathyroidectomy guided by gland size as opposed to intraoperative PTH monitoring had a higher incidence of multiglandular disease (10 % versus 0 %, respectively) [20]. The operative success rate was equivalent between the two groups, despite fewer glands being removed in the group who underwent parathyroidectomy guided by function as opposed to gland morphology. The potential risks of bilateral neck exploration are not trivial, including persistent hypocalcemia, recurrent laryngeal nerve injury, and fibrosis and scarring making revision surgery more difficult. Conversely, focused parathyroidectomy guided by intraoperative PTH monitoring leads to equivalent cure rates with shorter hospital stays and reduced cost when compared to traditional bilateral neck exploration [35]. Therefore, the use of intraoperative PTH monitoring to guide parathyroidectomy as opposed to bilateral neck exploration is an important surgical asset.

Alternative Applications for Intraoperative PTH Assays

Fine-Needle Aspiration Analysis

PTH levels obtained from fine-needle aspirates during parathyroidectomy can differentiate parathyroid from non-parathyroid tissue with a specificity of 100 % [36, 37]. To perform this technique, a 25-gauge needle attached to a 10 cc syringe is used to aspirate cells from the suspicious tissue. This aspirate is then analyzed for PTH using the same rapid PTH assay already employed in that laboratory. Pelizzo *et al.* measured rapid intraoperative PTH values on 50 structures presumed to be either parathyroid glands or lymph nodes that were then sent for frozen section analysis. They found that the median PTH value of parathyroid tissue was 263.25 pmol/L compared to a median PTH of 1.31 pmol/L from lymph node tissue ($p < 0.0001$; [36]).

Internal Jugular Venous Sampling

For patients in which preoperative imaging is equivocal, differential internal jugular venous sampling can help the surgeon to determine the laterality of a hypersecreting parathyroid gland. Blood samples are obtained from both internal jugular veins, preferably under ultrasound guidance prior to incision, and sent for PTH analysis. Studies have shown that the side harboring a hypersecreting parathyroid gland has an approximately 10 % higher PTH level compared to the contralateral side [38–40]. This allows the surgeon to start on the side of the neck with the higher PTH level and potentially avoid bilateral neck exploration.

Summary

Intraoperative PTH monitoring is now a commonly utilized tool in the surgical management of patients with sporadic primary hyperparathyroidism. Its use during parathyroidectomy guides the surgeon in operative decision making and is often a critical aspect of the surgery itself. The use of intraoperative PTH monitoring has several benefits over traditional bilateral neck exploration, including shorter operative times and hospital stays and the reduced potential for complications. Most surgeons recommend using a greater than 50 % PTH drop criterion from the pre-incision PTH value to a 10-min post-excision PTH value for measuring operative success. Additionally, many surgeons recommend a post-excision PTH value that returns to the normal reference range. This criterion has improved accuracy in identifying parathyroid adenomas with reduction of unnecessary bilateral neck exploration. Further investigation is required into the utility and efficacy of intraoperative PTH monitoring for parathyroid disorders other than sporadic primary hyperparathyroidism.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion
Intraoperative PTH monitoring is a safe and effective adjuvant to parathyroid surgery, particularly for patients with sporadic primary hyperparathyroidism. However, its effective use relies upon the surgeon's thorough knowledge of parathyroid hormone physiology and standardization of the intraoperative protocol.

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Intraoperative Parathyroid Ultrasound

23

Ryan J. Li and Lisa A. Orloff

Contents

Introduction

An introduction to the fundamentals of ultrasound is provided elsewhere in this book (Chap. 13). Here we review some of the basic principles of ultrasound that make this imaging modality a very useful instrument in the management of parathyroid disease. A more in-depth description of ultrasound fundamentals can be found within several dedicated textbooks of ultrasonography [1, 2]. Sound waves require a medium through which to propagate. Various mediums demonstrate differing impedance properties and speed at which they propagate sound based upon their density and composition. The difference in impedance of adjacent mediums results in the reflection of sound waves, a principle that allows for high-resolution imaging of anatomical structures in the neck with various natural densities. The computing power of an ultrasound machine infers the distance away from the ultrasound transducer that an object is located based upon the time elapsed from emission of a sound wave from the transducer until the reflected wave returns to the transducer. Along with the propagation and reflection of ultrasound waves, a third important property of sound travel is the degree of attenuation of the wave, which increases the farther from the transducer the wave propagates. The higher the frequency utilized in ultrasound, the earlier the attenuation and shorter distance of

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propagation through tissues; yet the resolution of imaging will be greater. The optimal frequency of ultrasound in parathyroid imaging, considering the need for high resolution and adequate depth of imaging, ranges from 7.5 to 13 MHz.

Ultrasound technology also takes advantage of the Doppler effect in evaluating vascular flow. The Doppler principle states that an object moving towards (or away) from the direction of a sound wave source will reflect the sound wave at a greater (or lower) frequency than the original emitted wave. This property is exploited by the ultrasound machine computations to determine both directionality and velocity of blood flow. A Doppler map is created by modern ultrasound systems that is superimposed on the B-mode (gray scale) ultrasound image to depict variations in blood flow within anatomic structures of interest, including pathologic parathyroid glands.

Indications for Parathyroid Ultrasound

Preoperative parathyroid ultrasound is one of the most frequently utilized imaging modalities in the evaluation of hyperparathyroidism, often providing stand-alone localization of abnormal parathyroid glands or complementary information to radionuclide scanning. The same preoperative utility of ultrasound can be applied to patients in the intraoperative setting when sonographic equipment is available. Whether the patient is under local or general anesthesia in preparation for surgery, he or she is in the appropriate operating head and neck position. The surgeon or other sonographer can then perform a thorough neck ultrasound examination to reconfirm the predicted location of the parathyroid lesion and plan an appropriate incision and approach. After excision of the parathyroid candidate, the surgeon can also ultrasound the specimen ex vivo to confirm that it resembles the candidate targeted preoperatively.

The indications for utilizing ultrasound in parathyroid disease are important to understand. All patients suspected of having primary hyperparathyroidism based upon history, exam, and laboratory workup, who are considered surgical candidates, are also candidates for both radionuclide scanning and neck ultrasound. Since approximately 85 % of patients with primary hyperparathyroidism will have a solitary parathyroid adenoma, localizing a target can be critical to surgical planning [3] (Fig. 23.1). In addition to evaluating the neck for one or more enlarged parathyroid glands, any potential thyroid pathology should also be evaluated by ultrasound prior to counseling the patient on the extent of surgery. Preoperative ultrasonographic evaluation of the thyroid gland directs further diagnostic testing that may then dictate a procedure that can be performed at the same time as parathyroid surgery [4]. Surgery of the central neck compartment is ideally performed at one session, as each subsequent surgery becomes more technically difficult and can raise the risk of operative morbidity [5, 6].

In patients suspected of having secondary or tertiary hyperparathyroidism, multigland hyperplasia is more commonly encountered than a solitary adenoma. Four-gland hyperplasia can usually be appreciated on ultrasound. In parathyroid hyperplasia, the four glands may not be uniformly enlarged, as one or more glands may demonstrate greater hyperplastic changes than the others [7–9] (Fig. 23.2). Ultrasound assessment may aid in planning the order of exploration, from the most prominently enlarged gland downwards, while following intraoperative PTH levels. Again thorough assessment of the thyroid gland will be important for planning the appropriate operation [10].

Neither radionuclide scanning nor parathyroid ultrasound exhibit absolute sensitivity nor specificity for parathyroid adenomas. A strongly localizing result from one image test may be sufficient to direct surgery, but it does not preclude an indication for radionuclide scanning or other imaging modalities [11, 12]. Identification of a cervical parathyroid adenoma candidate on ultrasound does not rule out the possibility of a second, ectopic adenoma in a location inaccessible to ultrasound (e.g., mediastinum, retropharynx). Whereas an ultrasound may reveal a hypoechoic lesion in an anatomically appropriate location for

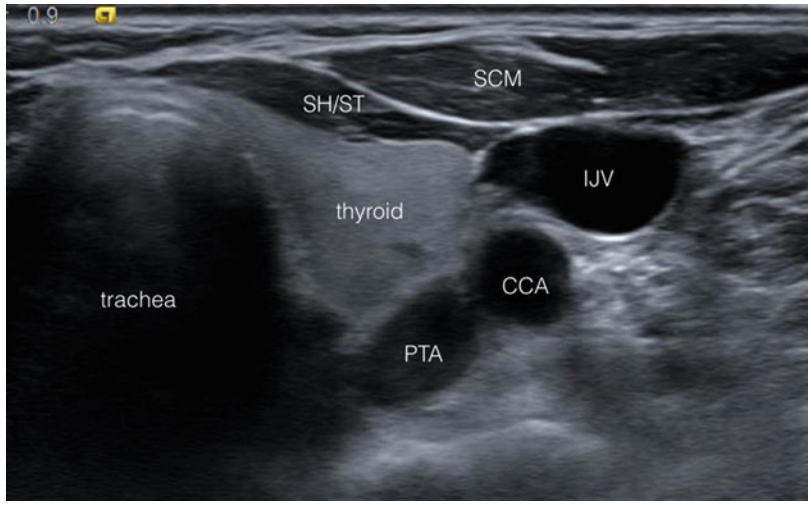

Fig. 23.1 Left inferior parathyroid adenoma abutting left common carotid artery and dorsal to left thyroid lobe. Transverse view. *CCA* common carotid artery, *IJV* internal jugular vein, *SH/ST* sternohyoid and sternothyroid muscles, *PTA* parathyroid adenoma, *SCM* sternocleidomastoid

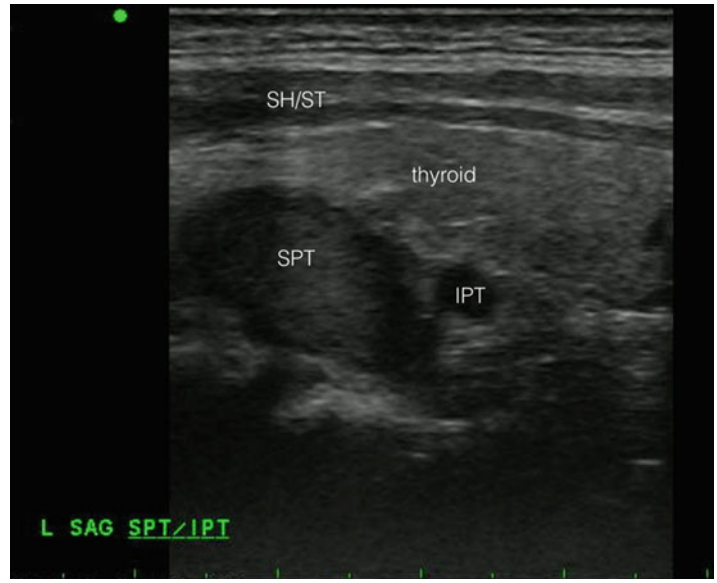

Fig. 23.2 Parathyroid hyperplasia showing a larger superior parathyroid and smaller inferior parathyroid gland. Both glands are hyperplastic but are asymmetrically enlarged. Sagittal view. *SPT* superior parathyroid, *IPT* inferior parathyroid, *SH/ST* sternohyoid and sternothyroid muscles

a parathyroid gland, a small lymph node may be difficult to distinguish from parathyroid tissue sonographically (Fig. 23.3). Sestamibi radionuclide scanning may help scrutinize a parathyroid candidate further with a functional evaluation. Conversely, a "positive" sestamibi radionuclide scan that suggests a sidedness to a parathyroid candidate is ideally supported by an ultrasound that demonstrates an enlarged hypoechoic lesion with the same laterality, as radionuclide scan interpretation is subject to distraction by background noise inherent to the properties of this imaging technique.

Preoperative or intraoperative ultrasound of the neck allows the surgeon to identify aberrant anatomy prior to the operation. For example a

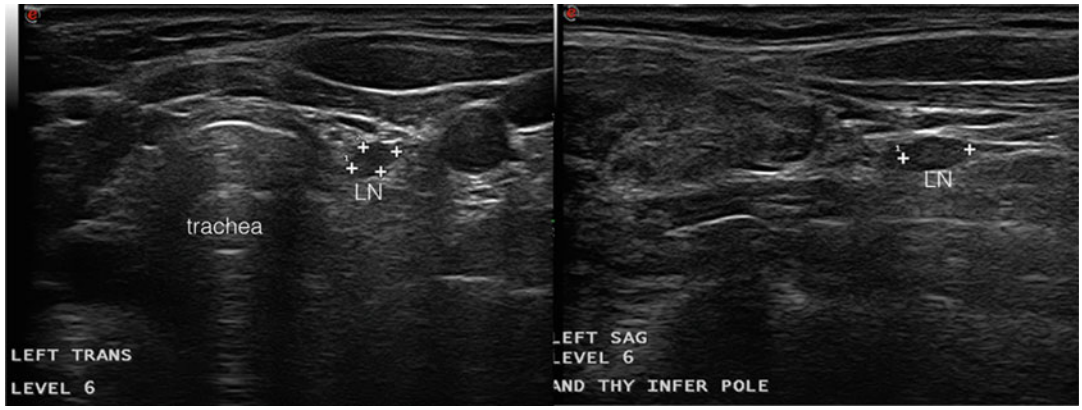

Fig. 23.3 Left level 6 lymph node. Transverse (*left*) and sagittal (*right*) views. *LN* lymph node

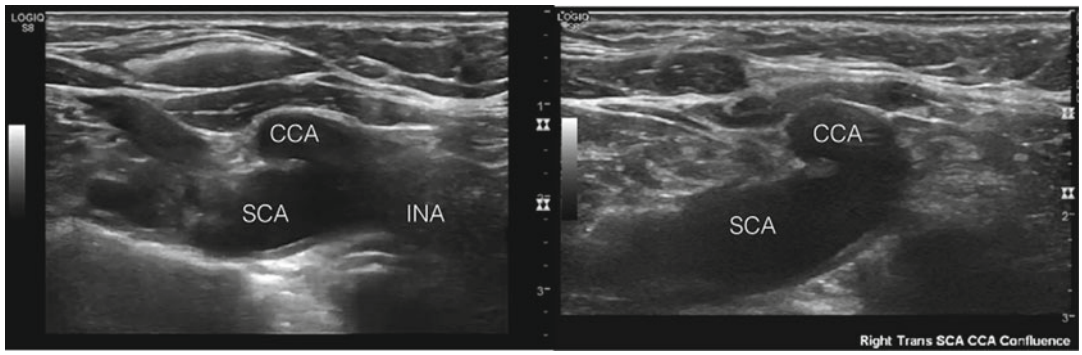

Fig. 23.4 Right common carotid and subclavian artery confluence. *CCA* common carotid artery, *SCA* subclavian artery, *INA* innominate artery

non-recurrent right laryngeal nerve is readily suspected if the right subclavian and carotid arteries do not proximally arise from an innominate artery, which should be identifiable on ultrasound in most patients [13]. While it is not necessary in all parathyroid cases to identify the recurrent (or non-recurrent) laryngeal nerve, its anatomical course should be understood and anticipated as well as possible in any central neck compartment surgery (Fig. 23.4 and Video 23.1).

Ultrasonographic Appearance of Parathyroid Tissue

Normal parathyroid glands are typically less than 40 mg in mass, and measure approximately 6 mm in cranio-caudad length, and 3–4 mm in width [3, 14]. They are typically too small and too similar to surrounding structures to be appreciated by ultrasound imaging. In the majority of cases, ultrasound imaging of pathologically enlarged parathyroid glands demonstrates a homogeneous ovoid, hypoechoic lesion that may have a distinct, more echogenic rim [15–17]. Less commonly, enlarged parathyroid glands may be multilobulated in shape; they may also appear anechoic, or even show echogenicity similar to thyroid tissue. The appearance may be difficult to distinguish from a lymph node, which also may be ovoid with a hypoechoic appearance. In enlarged lymph nodes, a fatty central hilum may be visible as a more echogenic region, and Doppler signaling for vascular flow should demonstrate central flow through the hilar vascular pedicle. In contrast, a parathyroid adenoma has a primarily polar vascular pedicle—rather than central within the ovoid mass; the pedicle typically terminates at the superior pole (Fig. 23.5 and Videos 23.2, 23.3, and 23.4). This may be best appreciated in sagittal ori-

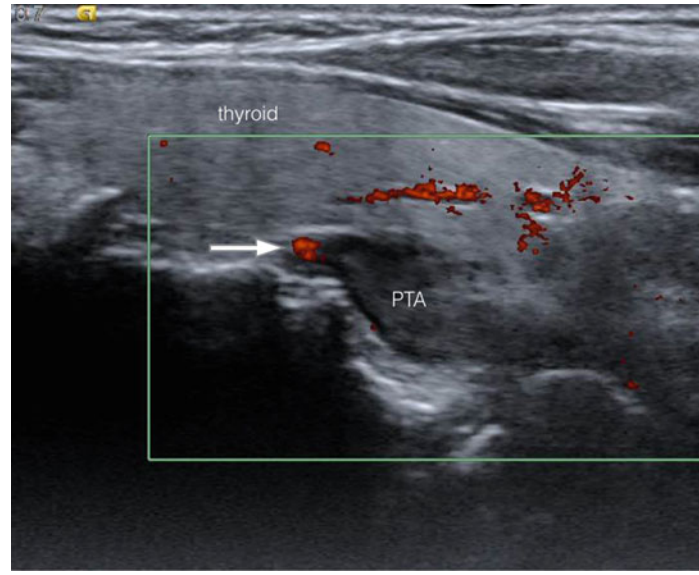

Fig. 23.5 Left inferior parathyroid adenoma showing superior polar vascularity (arrow). Sagittal view. *PTA* parathyroid adenoma

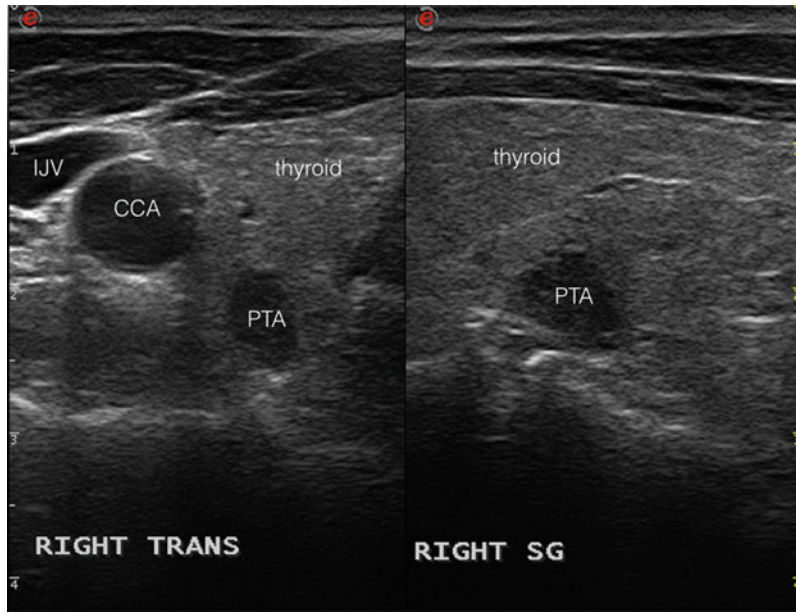

Fig. 23.6 Right intracapsular parathyroid adenoma. Transverse (*left*) and sagittal (*right*) views. *PTA* parathyroid adenoma, *CCA* common carotid artery, *IJV* internal jugular vein

entation on ultrasound. A vascular "arc" has also been described coursing over the surface of parathyroid tissue [18]. Hypervascularity of the parathyroid capsule, or hypervascularity of the adjacent thyroid gland, has also been reported on ultrasound Doppler flow studies [19]. The contrasting vascular characteristics of lymph nodes and parathyroid adenomas are difficult to discern in small lymph nodes, in which ultrasonographic resolution is insufficient to visualize the central hilum clearly.

A parathyroid candidate on ultrasound may also be difficult to distinguish from a thyroid nodule if an intracapsular parathyroid gland is suspected (Fig. 23.6). While echogenicity of the lesion may be somewhat helpful, many thyroid nodules are hypoechoic, round, or ovoid in appearance. Ordinarily a subcentimeter thyroid

nodule without suspicious characteristics (e.g., microcalcification, irregular borders) may not warrant a fine-needle aspiration (FNA) biopsy. However if such a nodule is a candidate for parathyroid tissue, an ultrasound-guided FNA biopsy with saline washings for parathyroid hormone (PTH) levels is a useful next diagnostic step, provided that accurate aspiration of the lesion is achieved [20, 21].

Patients diagnosed with primary hyperparathyroidism will be found to have a solitary adenoma in 85 % of cases; multigland disease, either diffuse hyperplasia or less commonly double adenomas in 15 % of cases; and in less than 1 % of cases, parathyroid carcinoma [3]. The key distinguishing factor between the rare parathyroid carcinoma and an adenoma on ultrasound is the invasion, by carcinoma, into adjacent structures that may be visualized on ultrasound, with an irregular lesion border. Physical exam findings of a palpable mass, and laboratory findings of a serum calcium greater than 14 mg/dL, a PTH greater than three times normal, and a markedly elevated serum alkaline phosphatase should also increase suspicion for parathyroid malignancy, although these each has low specificity [22, 23]. In multiple endocrine neoplasia types I and IIa, as well as secondary and tertiary hyperparathyroidism, multigland hyperplasia is typically appreciated on ultrasound, whereas sporadic cases of multiglandular disease may not present with enlarged parathyroid glands to a size visible on ultrasound.

Embryology and Location of the Parathyroid Glands

A brief review of the embryologic development of the parathyroid glands is useful to aid in understanding their most common anatomical locations and methodically survey potential ectopic sites for ultrasonographic identification. The superior and inferior parathyroid glands develop from the dorsal wings of the embryonic fourth and third pharyngeal pouches, respectively. Differentiation into parathyroid parenchyma occurs during the fifth to sixth week of gestation, followed by detachment from the pharynx at week 7 after which both pairs of glands begin a caudal migration. The superior parathyroid glands attach to the thyroid and migrate caudally for a much shorter distance than the inferior parathyroid glands. The superior parathyroid glands typically deposit along the posterior aspect of the mid to superior thyroid lobe. Whereas the inferior parathyroid glands develop from the dorsal wing of the third pharyngeal pouch, the thymus develops from the ventral wing of this same pouch. As the thymus migrates caudally into the superior mediastinum, the attached inferior parathyroid glands follow; however they usually detach from the thymus and deposit proximally, just inferior and posterior to the inferior thyroid pole.

The superior parathyroid gland is located posterior, or dorsal, to the recurrent laryngeal nerve (RLN), whereas the inferior parathyroid rests anterior, or ventral, to the nerve. Since the RLN is not visualized on parathyroid ultrasound, the posterior, or deep, border of the carotid artery or the inferior thyroid artery serves as sonographic surrogate landmark for the plane of the RLN (Figs. 23.7 and 23.8). For example a parathyroid candidate lying anterior, or superficial, to this plane would likely be an inferior parathyroid.

During a parathyroid ultrasound survey, it is helpful to anticipate typical and ectopic locations of parathyroid glands based on their embryological development. The superior parathyroid glands may be identified as high as the hyoid bone or level of the carotid bifurcation. In addition to the central compartment proper, ultrasound should examine the carotid sheath, retropharyngeal, retroesophageal, retrotracheal, and parapharyngeal spaces to the extent possible for potential ectopic glands [24]. The superior parathyroid gland may also descend into the posterior mediastinum, a space bounded superiorly by the upper border of pericardium, and inferiorly by the diaphragm, beyond visibility by transcutaneous ultrasound. The inferior parathyroid gland may continue to descend into the superior, or even anterior (anteroinferior) mediastinum as it follows the

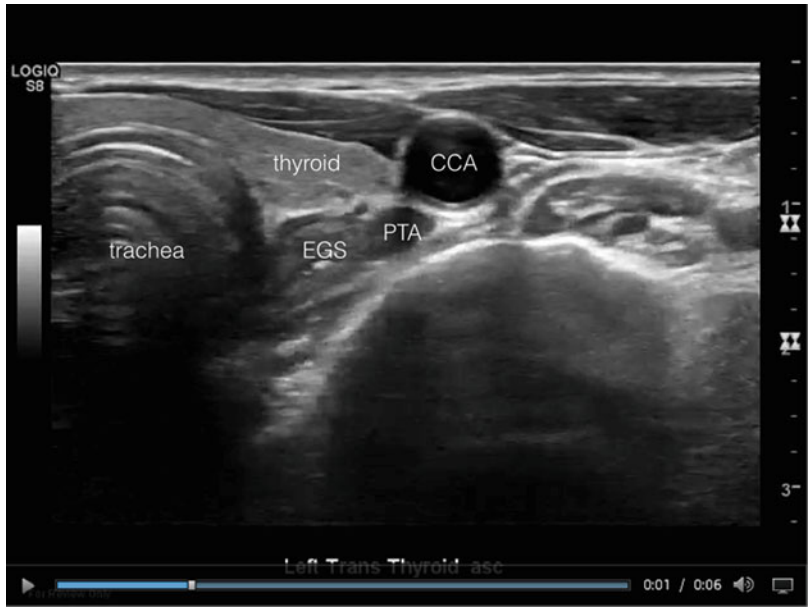

Fig. 23.7 A descended left superior parathyroid adenoma, abutting esophagus deep to posterior plane of the common carotid artery. Intraoperatively, the recurrent laryngeal nerve was identified ventral to the adenoma, as expected in relation to a superior parathyroid gland. Transverse view. *PTA* parathyroid adenoma, *CCA* common carotid artery, *EGS* esophagus

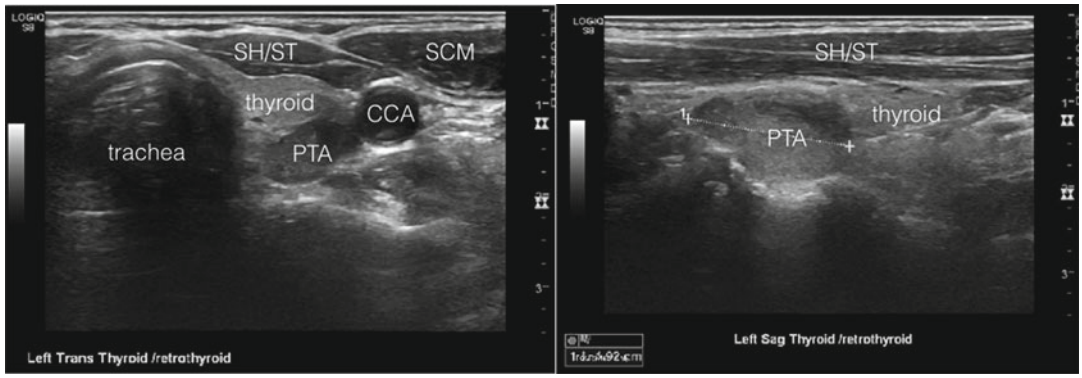

Fig. 23.8 Left superior parathyroid adenoma. Transverse (*left*) and sagittal (*right*) views. *PTA* parathyroid adenoma, *CCA* common carotid artery, *SCM* sternocleidomastoid, *SH/ST* sternohyoid and sternothyroid muscles

descent of the thymus. The inferior parathyroid gland may be found as far cephalic as the hyoid bone as well if it failed to descend with the thymus. A parathyroid candidate at this cephalic limit would be considered inferior or superior based on its relationship to the RLN.

Techniques in Parathyroid Ultrasound

Ultrasound evaluation of parathyroid disease should first begin with a thorough survey of the central neck compartment, from hyoid bone

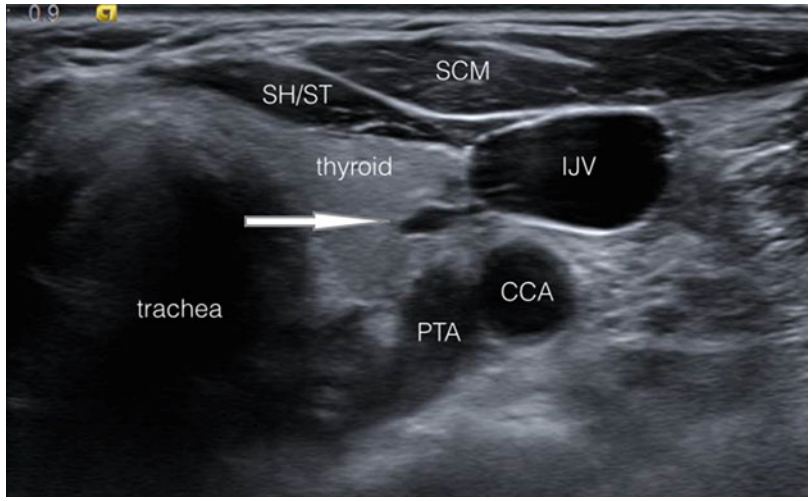

Fig. 23.9 Left inferior parathyroid adenoma. The left middle thyroid vein (*arrow*) is seen exiting the left mid-thyroid lobe, draining into the internal jugular vein. Transverse view. *PTA* parathyroid adenoma, *CCA* common carotid artery, *SCM* sternocleidomastoid, *SH/ST* sternohyoid and sternothyroid muscles, *IJV* internal jugular vein

cephalically to the thoracic inlet as far caudally as can be accessed by the ultrasound transducer [18]. A suggested approach begins by identification of the innominate artery as it courses from the superior mediastinum towards the right central neck compartment, branching into the right common carotid and subclavian artery. The space from right carotid sheath to larynx and trachea is carefully examined in a caudal to cephalad direction with the transducer in a transverse orientation. Examination continues to the superior limit of the thyroid lobe, and can extend to the hyoid. Any parathyroid candidates are then investigated with the transducer in a sagittal plane, which aids in visualizing the vascular pedicle that frequently can be seen at the superior pole of the enlarged gland. Examining the right central neck compartment beginning at the right innominate artery also provides rapid confirmation of the normal great vessel anatomy, and therefore RLN anatomy. The awake patient can be asked to turn his or her head towards and away from the examiner to further enhance visualization of otherwise overlapping structures; in the sedated patient, the examiner may need to carefully rotate the patient's head to accomplish the same result. An awake patient can also be asked to swallow, which can aid in distinguishing the esophagus from other nodular structures. The anesthetized patient may have an endotracheal tube and/or an esophageal probe in place that can distort anatomy or create ultrasound artifacts, such as acoustic shadowing, and should be noted.

The left central neck compartment is subsequently evaluated from the thoracic inlet to superior limit of the thyroid lobe, again from carotid sheath laterally to the trachea and larynx medially. Both transverse and sagittal transducer orientations are employed. Next the thyroid gland itself is evaluated, beginning with the right thyroid lobe from caudal to cephalad, transversely, and then in sagittal view. This step is repeated on the left, followed by examining the isthmus. As discussed earlier, it is worthwhile to perform thyroid ultrasound in all hyperparathyroidism patients, both in search of ectopic intrathyroidal parathyroid glands and to assess possible thyroid pathology that may warrant further diagnostic and therapeutic measures. Ultrasound-guided FNA biopsy of suspicious intrathyroidal lesions with saline needle washing for PTH assay can then be employed [21]. Often the middle thyroid vein is seen draining from the mid to lower thyroid lobe, and is a useful surgical landmark that may help orient the surgeon if a parathyroid candidate is visualized nearby (Fig. 23.9).

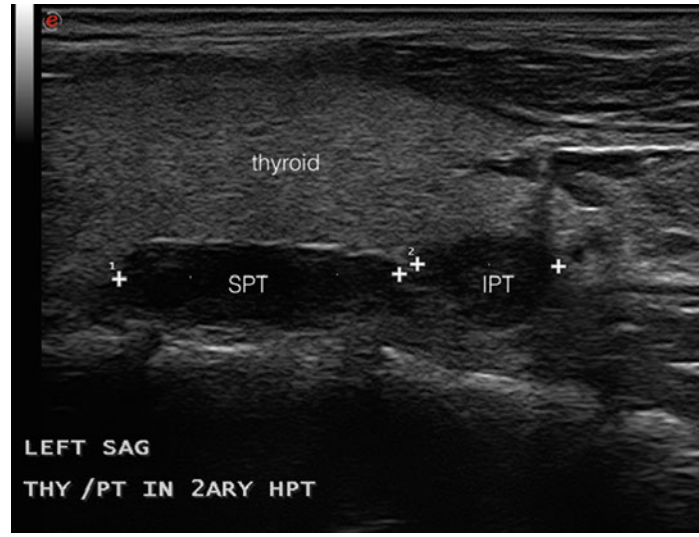

Fig. 23.10 Parathyroid hyperplasia, superior greater than inferior. Sagittal view. *SPT* superior parathyroid, *IPT* inferior parathyroid

Ultrasonographic visualization beyond the thoracic inlet into the superior mediastinum is often limited by patient habitus, and sometimes can be facilitated by sagittal positioning of the transducer, leading with one corner of the transducer. Deep planes, including potential ectopic sites such as prevertebral, and retropharyngeal, retroesophageal, and retrotracheal spaces, may require adjustments of the ultrasound settings to a lower frequency, which allows for better penetration of sound energy due to longer wavelength. The ultrasound field gain (either overall gain or time-gain compensation in the far field) is increased for deeper examination as well. In addition to an anteroposterior direction of transducer placement, a lateral approach is employed to examine these "retro-aerodigestive" spaces with less impedance from the carotid artery and laryngotracheal framework. After parathyroid candidates have been identified, Doppler flow can be utilized to assess for typical vascular patterns, such as a polar vascular pedicle, a vascular arch, or increased adjacent thyroidal vascularity.

The surgeon or sonographer should avoid quick conclusions about the location of the pathologic parathyroid gland based upon prior knowledge of radionuclide findings, as this bias can lead to a less thorough examination of the entire space at risk for harboring parathyroid disease. Even in cases of multigland hyperplasia, one parathyroid gland may be larger than the other three, and lead to the assumption that the patient has a solitary adenoma (Fig. 23.10). Rather the surgeon or radiologist can use the full potential of ultrasound to map out the entire at-risk neck spaces.

Current Investigations into Parathyroid Ultrasound

As discussed earlier, preoperative radionuclide scanning and neck ultrasound provide complementary information that is pivotal for surgical planning in primary hyperparathyroidism. For both preoperative and intraoperative ultrasound, the experience and motivation of the sonographer are vital attributes in determining the quality and validity of an exam [25–28]. For the patient with primary hyperparathyroidism who is suspected of having a solitary adenoma on ultrasound, the sonographer can help direct the tailoring of a small, targeted incision by specifying the most likely central neck quadrant and triangulating location with respect to regional anatomy for a minimally invasive surgical approach [29] (Figs. 23.11 and 23.12 and Video 23.5). The surgeon must plan an incision that can be extended if necessary, such that both surgical exposure and final cosmesis are optimized. While other imag-

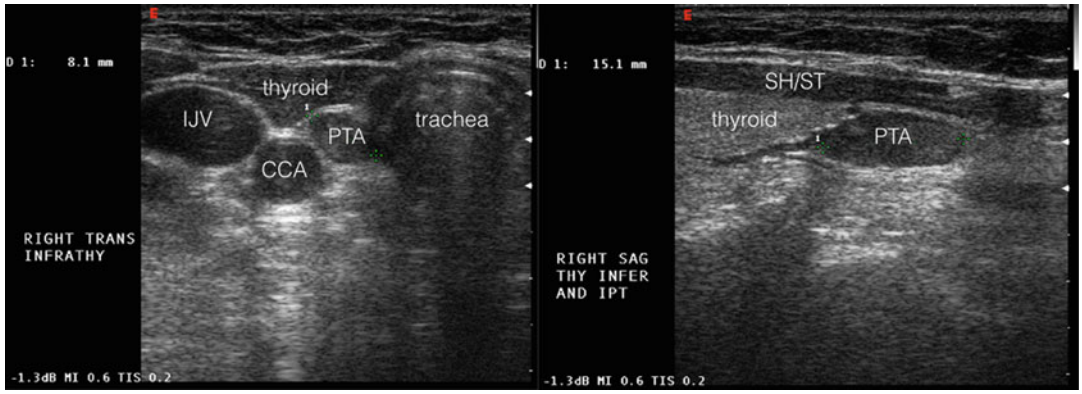

Fig. 23.11 Right inferior parathyroid adenoma, transverse (*left*) and sagittal (*right*) views. *PTA* parathyroid adenoma, *CCA* common carotid artery, *SH/ST* sternohyoid and sternothyroid muscles, *IJV* internal jugular vein

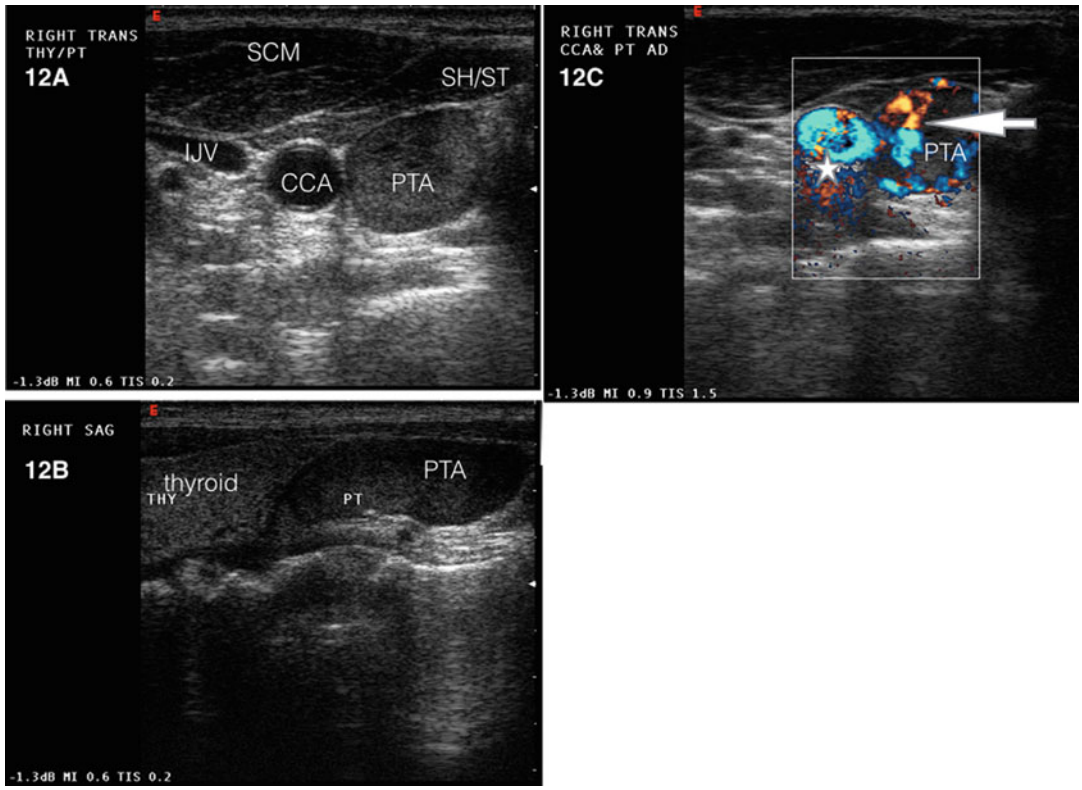

Fig. 23.12 Large right inferior parathyroid adenoma. Transverse view (12A); sagittal view (12B); Doppler shows hypervascular pattern of the adenoma, adjacent to the high flow of the common carotid artery (12C—arrow marks PTA, star marks CCA). *PTA* parathyroid adenoma, *CCA* common carotid artery, *SH/ST* sternohyoid and sternothyroid muscles, *IJV* internal jugular vein, *SCM* sternocleidomastoid. *On sagittal view, left side of image is cephalad, right side is caudal

ing modalities can also potentially localize an adenoma to the correct quadrant (e.g., MRI, CT, 4D CT, sestamibi), none has the low cost, speed, and/or non-radiation-based advantages of ultrasound.

Some surgeons have endorsed the use of adjunctive intraoperative localizing procedures such as ultrasound-guided, intralesional methylene blue dye injection, particularly in reoperative necks in which the normal tissue planes can be significantly altered [30, 31]. This technique of tattooing the suspected parathyroid adenoma is logical; however it must be implemented with precision. As a dry, bloodless field is essential in parathyroid surgery, any staining of methylene blue into tissues surrounding the candidate adenoma can blur tissue interfaces. As an endocrine gland that is primarily secreting hormone into systemic circulation, successful injection of the parathyroid may be followed by egress of blue dye through the gland's venous outflow into surrounding tissues, again obscuring planes of dissection.

The application of ultrasound in parathyroid hyperplasia has also been investigated as a potential quantitative instrument for preoperatively calculating the extent of gland excision necessary in the preoperative setting. While this concept requires further investigation in larger patient cohorts, a recent study of ten patients with multiple endocrine neoplasia type I showed a positive correlation between total calculated parathyroid volume on preoperative ultrasound and preoperative serum intact parathyroid hormone (iPTH) level ($R=0.96$, $P<0.001$) [32]. The investigators derived a formula directly relating sonographic parathyroid volume and iPTH (volume in $mm^3 = 15 \times iPTH\ (pg/mL) - 1000$). They postulated a scenario in which such a correlation could be useful. If a patient with parathyroid hyperplasia is also found to have a thyroid lesion (i.e., nodule versus intrathyroidal parathyroid), a simple calculation of parathyroid volume by preoperative ultrasound, compared to the volume predicted by the above formula, might suggest the probability that the intrathyroidal lesion represented functional parathyroid tissue. Future studies with larger patient cohorts may better validate this proposed correlation. Ultimately an intraoperative determination by the surgeon for adequacy of four-gland exploration is necessary, but innovative approaches to preoperative planning are helpful for the surgeon to anticipate the course of surgery, and provide patient counseling. Likewise in cases of parathyroid hyperplasia associated with secondary and tertiary hyperparathyroidism, while preoperative ultrasound does not replace a thorough four-gland exploration, evaluation of the thyroid gland for concomitant pathology (or ectopic parathyroid tissue) is key to operative planning prior to making an incision [10].

There remains a need for high-resolution imaging modalities to visualize the retropharynx, retroesophagus, and mediastinum—potential sites for ectopic parathyroid tissue that are not easily visualized with percutaneous transcervical ultrasound. MRI or CT imaging may complement sestamibi in identifying such ectopic parathyroids. Preoperative endoscopic ultrasound has also been described to interrogate these anatomical locations, and can also be combined with a fine-needle aspirate measuring PTH levels [33, 34]. To our knowledge only case reports have described the usage of endobronchial ultrasound (EBUS) to identify and plan excision of mediastinal and retroesophageal parathyroid adenomas. However EBUS-assisted FNA has been widely utilized to diagnose mediastinal masses prior to surgical intervention [35]. In patients with persistent hyperparathyroidism after a thorough prior neck exploration (e.g., with parathyroid adenoma excision), detection of a suspected ectopic hyperfunctional parathyroid may be facilitated by endoscopic ultrasound.

Summary

Localization studies have been described as preoperative tools for the surgeon to use only after a biochemical diagnosis of hyperparathyroidism has been made and surgery recommended. Increasingly, however, parathyroid surgeons are knowledgeable of and adept at utilizing the advantages of real-time ultrasonography for pre-

cise assessment of pathologic parathyroid glands in the context of the associated surgical anatomy. In equivocal, asymptomatic, or early cases of hyperparathyroidism, a preoperative ultrasound that fails to reveal a candidate for a pathologic parathyroid gland, especially in the setting of a nonlocalizing sestamibi parathyroid scan, might appropriately lead the clinician to postpone surgery or consider ancillary studies for localization. On the other hand, a finding of thyroid pathology in addition to localization of parathyroid candidate(s) with ultrasound may lead to expansion of the surgical plan. Once the decision has been made to operate, the use of ultrasound in the operating room immediately prior to incision can significantly enhance surgical strategy. After an incision has been made, ultrasound can still be performed through adjacent skin using a sterile or sterilely draped transducer, and intracavitary ultrasound, although difficult within the minimal access incision, can be used to confirm a target. Back table ultrasound of excised specimens can further help to confirm retrieval of intended targets.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion
Ultrasound can be relied upon at multiple phases in the care of the patient with hyperparathyroidism, enabling characterization of and vision through, not just around, anatomical structures.

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Re-operative Parathyroid Surgery

24

Jonathan Mark and David Steward

Contents

Introduction

Re-operative parathyroid surgery can result from prior thyroid or low anterior cervical spine surgery which can result in difficulty due to scar but otherwise similar to primary parathyroidectomy, or prior parathyroid surgery which is much more nuanced. Surgically managed sporadic primary hyperparathyroidism has reported success rates exceeding 95 % [1]. Despite the high success rate, some cases require re-operation, especially with hereditary primary or chronic renal failure-related secondary hyperparathyroidism. When a patient remains hypercalcemic and hyperparathyroid within 6 months following initial parathyroid surgery, they are considered to have persistent primary hyperparathyroidism. Recurrent primary hyperparathyroidism may occur after initial successful parathyroidectomy and postoperative period of normocalcemia. Over time, less invasive surgical techniques coupled with preoperative localization studies have shifted many initial operations away from initial four-gland exploration. Most commonly the cause of persistent hyperparathyroidism in a patient with sporadic primary hyperparathyroidism is a missed parathyroid adenoma (solitary or second) or unrecognized hyperplasia. A missed solitary adenoma may be easily treated with accurate preoperative localization and an experienced surgeon. Non-localized persistent disease and/or multigland dis-

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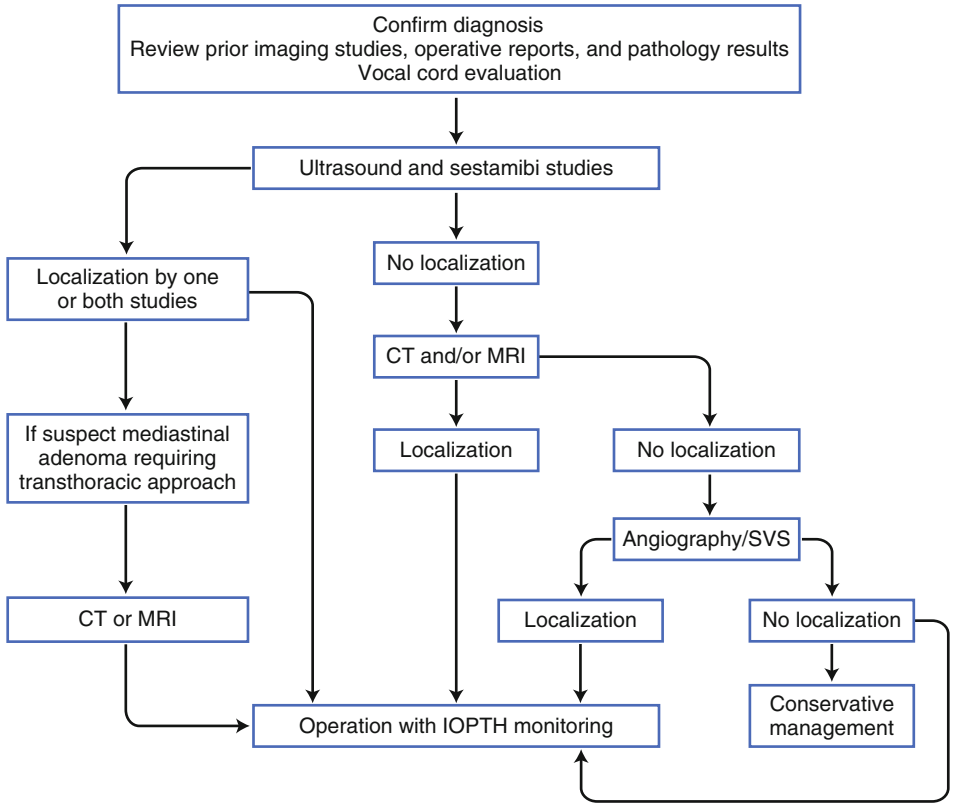

Fig. 24.1 Algorithm for preoperative localization workup in recurrent or persistent hyperparathyroidism [2]

ease can be substantially more challenging. Persistent or recurrent primary hyperparathyroidism can eventually lead to complications similar to untreated primary hyperparathyroidism; however given the difficulty of re-operation, a reassessment of the indications and necessity of revision surgery is warranted (Fig. 24.1).

When re-operative parathyroid surgery is necessary, it has been historically associated with an increased risk of vocal fold paresis and permanent hypoparathyroidism [2], as well as lower cure rates compared with primary surgery [3]. Thus an "ounce" of prevention in primary parathyroid surgery is worth a "pound" of cure with revision surgery. While parathyroid imaging for preoperative localization has improved greatly over the past 2 decades, John Doppman's observation that "the greatest challenge in parathyroid localization is to localize a good parathyroid surgeon" [4] holds true, especially within the context of revision surgery. Prior to embarking on re-operative parathyroid surgery, the surgeon should (1) review the prior and current biochemical workup to confirm the diagnosis, and (2) review the prior operative, pathology, imaging, and intraoperative PTH results in attempt to understand the extent of original surgery and potential cause for failure. Parathyroid embryology and anatomy, intraoperative PTH monitoring, preoperative imaging, radiopharmaceutical guidance, jugular venous sampling, and RLN monitoring are all important considerations and adjuncts which may be helpful in re-operative parathyroid surgery. Lastly, a modified lateral approach avoiding scar tissue from prior surgery is helpful when possible [5].

Preoperative Workup

Indications

The indications for re-operative parathyroidectomy are technically the same as for initial exploration;

however given the higher operative risks and lower likelihood of cure, a thoughtful evaluation of the risks and benefits of surgery as well as alternative treatment options is imperative. It is important to confirm that the patient has symptoms that justify further surgery or may suffer end-organ damage such as bone disease or renal stones if left untreated.

Differential Diagnosis

It is important to confirm the diagnosis of primary hyperparathyroidism and consideration should be given to familial hypocalciuric hypercalcemia, secondary hyperparathyroidism from vitamin D deficiency, or other causes of hypercalcemia, which would not benefit from revision surgery. In patients with confirmed persistent or recurrent primary hyperparathyroidism, consideration for hereditary etiologies such as MEN1, MEN2a, or hyperparathyroid jaw tumor syndrome should be considered, as well as the possibility of an incompletely excised adenoma or parathyroid carcinoma.

Due Diligence

Biochemical confirmation of persistent hyperparathyroidism should be obtained. Review of prior records (operative, pathology, laboratory, and imaging) to ascertain the findings and extent of the procedure carried out at the initial operation including which parathyroid glands were identified and removed should be clarified. Additionally, areas which were and were not explored should be defined. Consider re-review of prior pathology slides. Assess preoperative vocal fold mobility, as the need for re-operation in a patient with unilateral vocal fold immobility should be carefully considered when weighing the risks and benefits of exploring the contralateral side.

Imaging Localization

It may be necessary to repeat localization scans.

Ultrasound

High-resolution ultrasound is an excellent method for preoperative localization of parathyroid adenomas in re-operative cases. Its utility has been established, despite the potential effect of scar tissue obscuring views of the tissue planes and vascularity important for identification of an adenoma. Ghaheri et al. reviewed their ultrasound localization results in re-operative explorations and found similar positive predictive values between patients with and patients without prior thyroid or parathyroid surgery, 84 % vs. 90 % [6]. In conjunction with ultrasound, fine-needle aspiration biopsy may be analyzed for intact parathyroid hormone (iPTH) for localization of the suspected abnormal parathyroid gland, especially when intrathyroidal [7].

Nuclear Medicine

Tc 99m-sestamibi scan (MIBI) using single-photon emission computed tomography (SPECT) with or without fusion CT is very helpful when available, but may have some institutional variability in sensitivity and specificity. Addition of the CT fusion adds better anatomical localization for surgical planning. In the re-operative setting the accuracy of the test is reduced. In patients with persistent hyperparathyroidism, MIBI SPECT accurately localized a pathological parathyroid gland in 33 % of cases before re-operative parathyroidectomy, compared to 61 % in a primary surgical setting [8]. Recently, reports of up to 79 % sensitivity for MIBI preoperative imaging have been given [9]. Multiglandular disease is challenging to detect; Siperstein et al. found that even when the preoperative location suggested a single adenoma, the final diagnosis for those US-identified single-gland patients was only correct 75 % of the time and 70 % of the time for MIBI patients. When MIBI and US were concordant, 16 % of patients were found to have additional parathyroid pathology on further exploration [10].

4D CT

"Four-dimensional" contrast-enhanced dynamic CT (4D CT) provides another modality of parathyroid localization. Generally the patient has a non-contrast CT, followed by iodinated contrast CT scans in both the early arterial and subsequent venous phases. Some concerns about increased radiation dose have been raised, although lower dose protocols have been used with success [11]. It may help identify multiglandular disease, which could be an advantage over MIBI imaging and can identify abnormal parathyroid glands missed by US and MIBI [12]. Additionally, it was not found to have an accuracy difference between primary and re-operative cases [13]. It does have the advantage over US of being able to image the mediastinum.

MRI

Enlarged parathyroid glands typically demonstrate increased intensity on T2-weighted images on MRI, but is generally less sensitive than US, MIBI, and/or CT in part due to long scan times and motion artifact related to swallowing and respiration. In one review of patients with persistent/recurrent hyperparathyroidism, MIBI was compared with MRI and found to have similar sensitivity and positive predictive value [14].

Venous Sampling and Angiography

When noninvasive techniques are unsuccessful, catheterization and blood sampling for PTH can provide information about the region of the pathologic gland. Angiography may reveal a blush localizing an adenoma. Experience with this technique is limited to specialized centers however.

Intraoperatively, bilateral inferior jugular vein sampling with (intraoperative PTH) intraoperative parathyroid hormone (IoPTH) can be helpful in indicating the laterality of hyperfunctioning parathyroid tissue. In cases where IoPTH samples were >5 % different from each other, hyperfunctioning parathyroid tissue was successfully localized, though the senior author finds at least a 50 % difference more convincing. This has been found to be especially useful for localization in the setting where initial removal of a suspected adenoma does not yield an adequate IoPTH response, or where preoperative imaging is non-localizing. This is a simple task if exposure for bilateral neck exploration is used [15]. It can also be performed in the office using US guidance. In cases of jugular vein PTH symmetry, the patient may have a mediastinal adenoma or bilateral multigland disease.

Operative Technique

Timing

Re-operation may be undertaken within a week of the initial surgery or postponed to greater than 3 months from the initial procedure. The strategy is to either avoid fibrosis and inflammation or allow it to subside and obtain further localization studies. Generally there is no rush to get back in unless the patient had undergone bilateral exploration with identification of all four glands and was undertreated with removal of only a single gland.

Strategy

After the diagnosis and indication for surgery are confirmed, localization studies assist in forming a strategy to approach the remaining diseased parathyroid tissue. MIBI/SPECT CT and US provide complementary information for localization and are good for initial investigation before re-operative cases. Discordant or non-localizing studies may prompt the need for alternative imaging, generally CT, or an invasive localization study if experience is available (Table 24.1).

Most re-operative parathyroid surgery is performed for a missed, solitary, eutopic adenoma [1, 9, 16, 17]. In a review by Richards et al. of 2065 patients who underwent parathyroidectomy for primary hyperparathyroidism, 228 patients

Table 24.1 Apply a systematic approach to the distribution of remaining disease

Distribution of remaining disease
Solitary gland
Ectopic/eutopic
Multiple abnormal glands
Ectopic/eutopic
Adenoma/hyperplasia
Supernumerary
Incomplete resection or parathormatosis
Incorrect diagnosis

(11 %) were identified that underwent re-operative procedures, the majority of which (57 %) were found to have solitary gland disease. The adenomas were typically located in eutopic position lateral to the thyroid gland [17]. It is notable that in this review 8.5 % of patients had MEN 1, which perhaps accounts for why this is skewed to represent multiglandular disease, and other reports describe up to 78 % of patients presenting with solitary disease in re-operative parathyroid surgery [9]. In another re-operative review of 237 patients adenomas were found in ectopic locations in 32 % of cases and were most frequently in the thymus [18].

Typical locations for ectopic parathyroid tissue have been described. Ectopic inferior parathyroid glands can vary in position due to abnormal descent from the third pharyngeal pouch during embryological development. Most commonly, ectopic inferior parathyroid glands are intrathymic, but they can also be mediastinal, and intrathyroidal, within the thyrothymic ligament, and in the submandibular triangle. Superior parathyroid glands are less variable in position. During embryologic migration the superior parathyroids migrate with the thyroid gland along a relatively short path arising from the fourth branchial pouch. Ectopic superior glands can be located in the tracheoesophageal groove, retroesophageal space, posterosuperior mediastinum, thyroid gland, carotid sheath, and paraesophageal [19]. The location of missed parathyroid glands was defined in a recent review. In a re-operative parathyroidectomy cases 5 (10 %) were adherent to the posterior thyroid capsule, 11 (22 %) were behind the thyroid in the tracheoesophageal groove, 7 (14 %) were close to the clavicle in the prevertebral space, 3 (6 %) were directly over the recurrent laryngeal nerve, 9 (18 %) were easy to identify near the inferior thyroid pole, 13 (26 %) had fallen into the thymus, and 2 (4 %) were within the thyroid gland [16].

In a review of the American College of Surgeons national surgical quality improvement program database (2008–2011), the annual rate of re-operation was 3.6–4.8 %. Patients undergoing re-operative parathyroid surgery were identified to more likely be obese, have a longer operative time, have a longer postoperative stay, and were more likely to be readmitted in 30 days [20].

Operative Technique

Operating in a neck with scar tissue and altered tissue planes can be challenging and carries a higher risk of complications. Due to the increased likelihood of a prolonged procedure and increased difficulty of the dissection, the operation is generally performed under general anesthesia. The surgical approach for re-operative parathyroid surgery should be designed to avoid dissecting through scar tissue if possible and tailored to the preoperative localization studies. Since most initial parathyroidectomies are performed through a midline approach mobilizing the strap muscles laterally and retracting the thyroid medially, re-explorations may need to be performed through a different approach. Fighting through scar tissue can result in bleeding from the surface of the thyroid and obscure the surgical field, as well as surgeon fatigue. Unilateral approach or bilateral neck explorations are considered for re-operation depending on the surgeon's confidence in the preoperative localization studies. If a prior midline approach was used, re-operation through the prior incision can be performed with a modified lateral approach by retracting the strap muscles and thyroid medially to avoid bleeding from peeling the straps off the thyroid. A midline incision facilitates a bilateral neck exploration if needed. In the lateral approach

the patient's head is turned contralateral to the adenoma side and dissection is carried out lateral to the strap muscles and medial to the carotid sheath. The recurrent laryngeal nerve can be identified more easily in virgin tissue using this approach. The vagus nerve can be easily identified and stimulated in the carotid sheath through this approach. Stimulation of the vagus can confirm that the nerve monitoring system is functioning and can be relied upon to help locate the recurrent laryngeal nerve. The anatomic and electrophysiologic algorithm for identification of the nonrecurrent laryngeal nerve entailing distal and proximal vagal nerve stimulation has been defined by Kamani et al. [21].

Preoperative or intraoperative US may identify an intrathyroidal parathyroid gland, which may be removed by thyroidotomy or through partial thyroidectomy. FNA of suspected intrathyroidal parathyroid for PTH testing can help identify pathologic parathyroid tissue [7, 22]. Hemithyroidectomy is preferable in cases of intrathyroidal parathyroid adenoma with coexistent nodular thyroid disease.

Intraoperative Parathyroid Hormone Monitoring

In general, monitoring of IoPTH can guide the operation in the same fashion as in first-time surgeries and accurately predict removal of hyperfunctioning parathyroid tissue. The use of the IoPTH monitoring assists in verifying resection of hyperfunctioning parathyroid tissue through an intraoperative drop in serum PTH levels by 50 % and to within the normal range. It is possible for the baseline IoPTH sample to be elevated relative to the levels in the preoperative workup because of surgical manipulation, depending on the timing of the blood draw. Peripheral venous access should be considered to facilitate a systematic approach to monitoring. If necessary, a delayed PTH level can be obtained for slow responders and may identify patients at risk for developing long-term hypoparathyroidism. If available, cryopreservation can be utilized or immediate reimplantation of parathyroid tissue can be considered. In a recent review of re-operative parathyroid surgeries, hypoparathyroidism was decreased using IOPTH monitoring [17] (Table 24.2).

Table 24.2 A sample of a chart for IoPTH monitoring is given

Time	PTH level
Incision	
Removal	
Removal + 5 min	
Removal + 10 min	
Removal + 15 min	
PACU	

Final IoPTH level may offer prognostic information. After parathyroidectomy for sporadic primary hyperparathyroidism, IoPTH levels for patients with a 50 % decrease and levels below 40 pg/mL had lower rates of persistence and recurrence compared to those with higher levels [23]. Intraoperative failure of IoPTH to decline 50 % and into normal range was associated with higher rates of multigland disease and smaller parathyroid glands [24]. In a review where all patients underwent eventual bilateral neck explorations, multiple-gland disease was not always detected with IoPTH. Localization studies and ioPTH failed to identify multiple-gland disease in 16 % of patients with sporadic primary hyperparathyroidism undergoing primary surgery [10]. Another group in which IoPTH may be more difficult to interpret is in renal patients. IoPTH monitoring in patients with chronic renal insufficiency demonstrated a slower decline in levels, but by 15 min met standard criteria for monitoring [25].

Gamma Probe

Gamma probe detection of radiolabeled sestamibi can assist in re-operative parathyroid surgery but is limited in directing dissection due to background signal from normal thyroid tissue [26]. It is most helpful is cases of prior thyroidectomy or when parathyroid tissue has been autotransplanted into muscle.

Methylene Blue

Use of a 7.5 mg/kg methylene blue infusion for intraoperative color localization of abnormal parathyroid tissue has been reported [27]. A case report supporting a lower dose of 4 mg/kg has also been reported following a rare occurrence of methylene blue toxicity at the higher dose [28]. Methylene blue has largely been abandoned due to MAOI toxicity in patients taking serotonin reuptake inhibitors [29] and due to nonselective staining.

Nerve Monitoring

A review of re-operative thyroid and parathyroid cases using intraoperative electromyographic monitoring of the recurrent laryngeal nerve did not show a reduction in nerve injury [30]. However, nerve stimulation can aid in nerve identification intraoperatively and is routinely used by the senior author.

Mediastinum

Mediastinal parathyroid tumors can typically be reached from a cervical approach and are addressed by being pulled up with the thymus through stepwise retraction. The extent of previous surgery may require alternative surgical approaches, but the ectopic parathyroid is typically accessible via a cervical approach; rarely patients may require exposure by either median sternotomy or thoracic approach. A rule tract retractor can aid in exposing the anterior superior mediastinum in cases where thymectomy fails to deliver the gland.

Complications

In a retrospective review, re-operative complication rates after initial minimally invasive parathyroidectomy and standard cervical exploration were compared. Higher rates of postoperative sequelae such as symptomatic hypocalcemia, surgical site infection, other infection, deep vein thrombosis, chest pain requiring cardiology consultation, new arrhythmia, or any issue that required emergency department evaluation or hospital admission were found to be lower in the group that initially had minimally invasive parathyroidectomy [31].

Summary

Summary with expert opinion for the chapter (senior author).

Re-operative parathyroid surgery requires a systematic preoperative workup with attention given to the biochemical confirmation of diagnosis, review of the operative notes, pathology, imaging, and intraoperative PTH results. The chance of cure in re-operative surgery is reduced and the chance of complication is increased in comparison to primary surgery.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion
It is incumbent on the surgeon to optimize chances of success utilizing available localization techniques, and by exercising careful, calculated clinical judgement.

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Surgery for Ectopic Parathyroid

25

Samuel K. Snyder

Contents

In 1927 Captain Charles Martell underwent the first cervical exploration for diagnosed primary hyperparathyroidism in America, but it did not identify an abnormal parathyroid gland. Multiple additional unsuccessful operations ensued until the patient himself insisted upon a mediastinal exploration to his surgeons after researching variable parathyroid gland anatomy at the Harvard Medical School library. At the 7th operation a 3 cm mediastinal parathyroid adenoma was resected. Unfortunately, the patient died from complications following ureteral stone surgery 6 weeks later. The sad saga of Captain Martell underscores the importance of understanding the variability of parathyroid anatomy and the locations of ectopic parathyroid glands when anticipating parathyroidectomy surgery for hyperparathyroidism [1, 2].

Embryology/Parathyroid Anatomy

Fetal development of the parthyroids materializes in the 5th week of gestation with the inferior parathyroids originating from the dorsal epithelium of the 3rd pharyngeal pouch with thymus gland originating from the ventral aspect. Both migrate inferiorly together with the parathyroid separating from the thymus gland to rest near the lower pole of the thyroid during the 7th week. The thymus and/or inferior parathyroid gland may fail to descend at all or together end up in

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the mediastinum well below the thyroid gland. The superior parathyroid gland originates from the dorsal epithelium of the 4th pharyngeal pouch and descends with the ultimobranchial body to reside close to the mid- to superior thyroid lobe. Likewise, the superior parathyroid gland can fail to descend or end up in a more posterior location near the thyroid with less cranial-caudal displacement than the inferior parathyroid gland [3, 4]. A Japanese review of the location of 23 ectopic parathyroid lesions discovered cranial/caudal variability in the location from the carotid bifurcation to the right paraaortic region and ventral/dorsal variability in the location from the surface of the sternohyoid muscle to the paraesophageal region [5]. The parathyroid surgeon needs to be aware of this anatomic variability when planning the initial surgery, completing the operative exploration, and evaluating for ectopic parathyroids after a failed cervical exploration.

The normal location of the inferior parathyroid gland is within 1–2 cm of the inferior/posterior/lateral surface of the inferior pole of the thyroid, frequently associated with the thyrothymic ligament. The parathyroid commonly is embedded in an envelope of loose fatty tissue. The inferior parathyroid is in this location about 80 % of the time. The inferior parathyroid can be frequently found near the cranial tip of the cervical extension of the thymus. The normal superior parathyroid gland is within 1–2 cm of the cricoid cartilage and thyroid cartilage junction on the posterior surface of the mid- to superior thyroid. This location occurs about 80 % of the time. Not uncommonly the superior parathyroid can be posterior to the superior pole 15 % of the time and occasionally just above the level of the tip of the superior pole posteriorly [6]. The superior thyroid blood vessels will sometimes need to be divided and the superior pole mobilized to expose the superior parathyroid gland. Commonly, the superior parathyroid gland will likewise be embedded in an envelope of loose fatty tissue. Cervical exploration necessitates looking in these common locations of the separate parathyroid glands first and then relying on mirror image locations for the contralateral parathyroids. The superior parathyroid glands are symmetrical 80 % of the time and the inferior parathyroid glands 70 % of the time [6]. As a general rule, the inferior parathyroid glands will be more superficially located, being anterior to the course of the recurrent laryngeal nerve. The superior parathyroid glands will be more posterior in location, typically near or posterior to the course of the recurrent laryngeal nerve [7]. The abnormal superior parathyroid gland is especially likely to be posterior to the recurrent laryngeal nerve.

Prevalence of Ectopic Parathyroid

The incidence of ectopic parathyroid will depend upon whether the parathyroid surgery is for primary or secondary hyperparathyroidism, parathyroid adenoma, or hyperplasia, and initial or reoperative parathyroid operation. A recent 10-year study of over 1500 parathyroidectomies found ectopic parathyroids in 22 % of patients. Excluding four gland hyperplasia and reoperations, this left 13 % of patients with ectopic parathyroid adenomas on the initial parathyroid exploration. Of these, 89 % were single adenomas, 11 % double adenomas. The predominant locations of the ectopic parathyroid were in the thymus (38 %), retroesophageal (31 %), and intrathyroidal (18 %) [8]. Another institution found 16 % of 231 patients with operated hyperparathyroidism had ectopic parathyroid glands, 62 % inferior parathyroid glands and 38 % superior parathyroid glands. The inferior parathyroid glands were located intrathymic (30 %), anterosuperior mediastinal (22 %), intrathyroidal (22 %), within the thyrothymic ligament (17 %), and submandibular (9 %). The superior parathyroid glands were located in the tracheoesophageal groove (43 %), retroesophageal (22 %), posterosuperior mediastinal (14 %), intrathyroidal (7 %), in the carotid sheath (7 %), and paraesophageal (7 %) [9]. One study comparing ectopic parathyroid adenomas to orthotopic parathyroid adenomas found the ectopic parathyroid adenomas to have significantly higher serum calcium levels (12.6 versus 11.4 mg/dl) and larger tumors (2.5 versus 1.9 cm) [10].

Unsuccessful initial operative localization of a parathyroid gland generally indicates an ectopic location for the parathyroid gland. Gough found ectopic parathyroid glands in 60 % of 28 patients with persistent hyperparathyroidism [11, 12]. Thyroid disease from a large multinodular goiter, thyroid cancer, inflammatory thyroid disease, vascular Graves' disease goiter, and extreme morbid obesity can make identification of normally located parathyroid glands very challenging. The location of a truly ectopic parathyroid gland can be congenital in origin, relating to arrested or abnormal fetal descent of the parathyroid gland. The ectopic location can also be acquired, relating to the size and weight of the abnormal parathyroid, which can be displaced by the effects of gravity, loose tissue planes, deglutition, and negative intrathoracic pressure. This occurs more often for the enlarged abnormal superior parathyroid gland (40 %) than the inferior parathyroid gland [13, 14]. The ectopic parathyroid gland can display all of the various parathyroid pathologies: benign adenoma, hyperplasia, parathyroid cyst, or parathyroid cancer. Sometimes the ectopic parathyroid gland can actually represent a supernumerary parathyroid [11, 15, 16]. Autopsy studies identify four parathyroid glands most of the time, with only three parathyroid glands 3–6 % of the time [3, 6, 17]. However, this could just represent difficulty in locating the 4th parathyroid gland. True extra parathyroid (supranumarary) glands are usually small and can be located close to the normal parathyroids or most commonly in the thymus gland [6]. Up to 8 or more parathyroid glands have been described. The incidence of extra parathyroids can be enhanced up to 10–15 % in patients with strong stimuli for parathyroid hyperplasia as occurs with Multiple Endocrine Neoplasia type 1, e.g. in the sternohyoid muscle [18], or secondary hyperparathyroidism associated with chronic renal failure [19, 20]. A 34-year study of subtotal parathyroidectomy including bilateral cervical thymectomy in 461 patients with renal hyperparathyroidism revealed ectopic intrathymic parathyroid glands in 39 % and supernumerary intrathymic parathyroid glands in 6.5 %. The frequency of these supernumerary intrathymic parathyroids was 7.4 % in patients on permanent hemodialysis, 3.9 % in predialysis patients, and 0 % in patients after successful kidney transplantation [21]. A smaller study of patients with end stage renal disease that were operated on for severe secondary hyperparathyroidism revealed ectopic parathyroid glands in 46 % of patients. Of these patients 14 % had supranumerary parathyroids [22]. The frequency of this occurrence has led some surgeons to recommend cervical thymectomy at the time of parathyroidectomy to reduce the incidence of recurrent or persistent hyperparathyroidism [6, 23].

Parathyroid Imaging

The advent of reliable imaging of abnormal parathyroid glands in the last 20 years has brought about directed minimally invasive parathyroidectomy for primary hyperparathyroidism. Another advantage of this imaging is to identify before the first cervical exploration an ectopic parathyroid gland that otherwise would not have been discovered surgically. In some cases the localization studies have led to directed excision of just the ectopic parathyroid gland. The imaging techniques currently of usefulness in the initial assessment of primary hyperparathyroidism are ultrasound, nuclear medicine scanning with technetium sestamibi, and 4D computed tomography (CT) scanning.

Ultrasound

The primary localization study is ultrasound by a radiologist or by the surgeon [24]. The latter approach is the author's preference (see Fig. 25.1). The parathyroid surgeon understands the normal anatomy and potential ectopic sites where an abnormal parathyroid gland can be seen by ultrasound to streamline surgical exploration [25]. Ultrasound can identify 60–70 % of abnormal parathyroids [26]. The technique utilizes a small parts transducer with resolution between 10 and 14 MHz. The higher the MHz, the better the spatial resolution and detail, but the more shallow the penetration. Therefore, ultrasound

Fig. 25.1 Parathyroid adenoma identified on office ultrasound

has the most utility in a patient with a relatively thin and lengthy neck, and least utility in a patient with a relatively thick and short neck or deep cervical location of the abnormal parathyroid gland. Sternoclavicular bone, tracheal or laryngeal cartilage, sizeable thyroid nodularity especially with calcifications, and edge shadowing from blood vessels; can all compromise cervical imaging of abnormal parathyroids glands with ultrasound. The ultrasonographer carefully searches the area posterior to the thyroid from the tip of the superior pole to the tip of the inferior pole. Discreet hypoechoic extrathyroidal densities posterior to the thyroid are almost certain to be an abnormal parathyroid gland. The larger the abnormal parathyroid gland the easier it is to image with ultrasound. It is very unusual to see lymphadenopathy posterior to the thyroid lobe, making any hypoechoic nodules in this location abnormal parathyroid glands. Ectopic locations identified for the superior parathyroid gland with ultrasound can be at the tip of the superior pole of the thyroid gland or a posteriorly descended parathyroid adenoma in a paraesophgeal prevertebral location, typically posterior to the inferior pole of the thyroid (see Fig. 25.2). Since 85–90 % of primary hyperparathyroidism is from a solitary adenoma, identifying ectopic superior parathyroid glands with ultrasound simplifies the minimally invasive approach guided by intraoperative parathyroid hormone monitoring. Specific sonographic techniques that aid the ultrasonographer in identifying the elusive parathyroid adenoma include (1) compression scanning, (2) color Doppler, (3) scanning regions where ectopic glands may be located, and (4) evaluating intrathyroidal adenomas [24].

The abnormal inferior parathyroid gland is generally easier to image with ultrasound since it is more superficial (ventral) in location, frequently up against the posterior/lateral surface of the inferior pole of the thyroid or just caudal to the inferior pole of the thyroid. Ectopic locations for the inferior parathyroid gland that can be seen with ultrasound are either intrathyroidal or intrathymic in the lower paratracheal neck. Intrathyroidal parathyroid glands are associated with the inferior parathyroid glands more than 90 % of the time and can be suspected in the setting of primary hyperparathyroidism [27, 28]. In many cases the abnormal intrathyroidal inferior parathyroid gland is actually just subcapsular within the inferior pole of the thyroid. This location can be suspected with ultrasound evaluation. If ultrasound-guided fine needle aspiration (FNA) of a truly intrathyroidal parathyroid is done for an apparent suspicious thyroid nodule, the cytopathologist will typically interpret the FNA as a follicular neoplasm, because of the lack of colloid in the specimen and uniform cytologic appearance of the cells. Knowing this fact should alert the surgeon to the possibility of an intrathyroidal parathyroid adenoma. The diagnosis can then be established with repeat ultrasound-guided FNA for parathyroid hormone (PTH) [29]. Two or three aspirates are dispersed into 1 ml of normal saline and submitted to the lab for PTH. A level identified to be more than two times the blood level is considered abnormal. Frequently the PTH level is many times the blood level. The FNA can be submitted for cytologic analysis with PTH staining to establish the diagnosis of an intrathyroidal parathyroid, but this is less reliable than FNA for a PTH level [30]. If aspiration of an intrathyroidal or extrathyroidal cystic nodule returns clear fluid, then a parathyroid cyst should be suspected [31]. The diagnosis can be confirmed by submitting this aspirate for PTH level determination.

When an intrathyroidal parathyroid adenoma can be established preoperatively, then the surgical approach can be modified to a thyroidotomy with excision of the parathyroid adenoma or

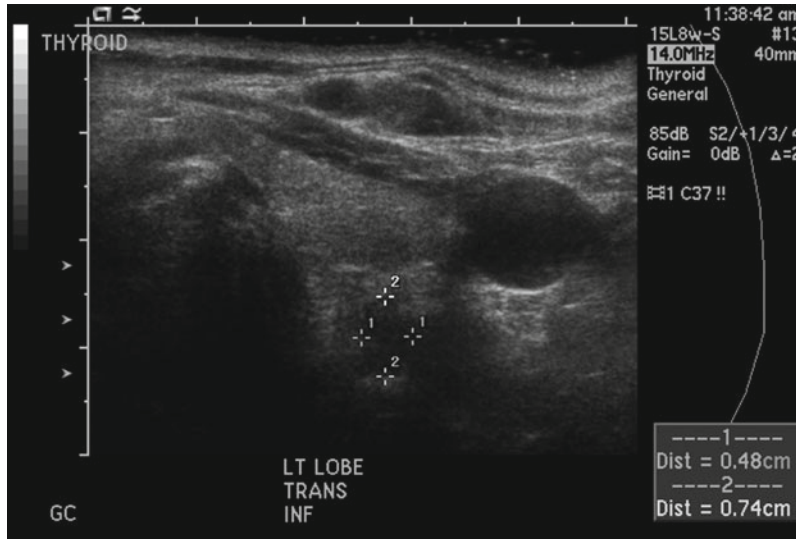

Fig. 25.2 Posteriorly descended left superior parathyroid adenoma on ultrasound

partial thyroidectomy of the inferior pole of the thyroid [32]. In a patient with a relative lengthy neck, the ectopic intrathymic parathyroid adenoma can be identified with ultrasound low in the neck in a paratracheal location. The distance from the tip of lower pole of the thyroid can be measured for reference and surgical guidance. Small adenomas in this location, however, can be confused with paratracheal lymphadenopathy. The diagnosis may also be clarified with ultrasound-guided FNA for PTH. Finally, ectopic inferior or superior parathyroid adenomas posterior to the carotid artery and within the carotid sheath can sometimes be imaged with ultrasound and thus direct surgical dissection.

If the central neck compartment does not contain a clearly imaged abnormal parathyroid gland, then the ultrasonographer needs to include the medial upper neck as part of the assessment for hyperparathyroidism. Either the inferior or superior parathyroid gland can have arrested embryologic descent and ultimately become abnormal. The upper neck frequently contains lymphadenopathy. These lymph nodes, however, are typically located just medial or lateral to the internal jugular vein in the upper neck and inferior to the submandibular salivary gland as level 2 lymph nodes. Benign lymph nodes can be distinguished by a focal hyperechoic area or stripe indicating the fatty hilum of the lymph node. An undescended parathyroid adenoma will lack the hyperechoic focus and be located typically medial to carotid artery. A common location is near the level of the bifurcation of the carotid artery [33]. A hypoechoic nodule imaged medial to the carotid artery close to the carotid bifurcation should be considered suspicious for an undescended parathyroid adenoma (see Fig. 25.3). The diagnosis can readily be confirmed with ultrasound-guided FNA for PTH like the evaluation for an intrathyroidal parathyroid adenoma. Gaining this information during the initial assessment of the neck for hyperparathyroidism, ultimately saves a long and frustrating central neck operation trying to locate a missing parathyroid gland and may limit collateral trauma to recurrent laryngeal nerves.

Another ultrasound-guided technique used to establish the presence of an undescended parathyroid is to obtain internal jugular venous blood samples from both veins to test for PTH [34, 35]. The side with an undescended parathyroid adenoma should have a level at least twice the peripheral baseline PTH.

Ultrasound has limitations in the central neck for identifying abnormal parathyroid glands. Parathyroid hyperplasia or small adenomas are more difficult to visualize. In addition, the deeper the parathyroid gland and the thicker the neck, the

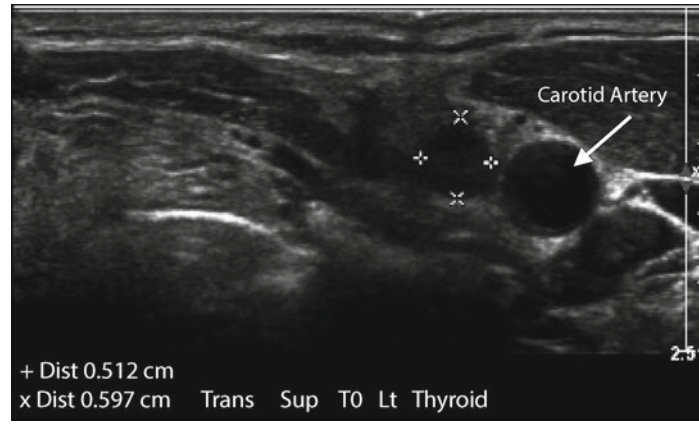

Fig. 25.3 Undescended left inferior parathyroid adenoma on ultrasound

more difficult imaging becomes. Thyroid goiter or nodules make imaging posterior to the thyroid difficult. Exophytic nodules off the posterior aspect of the thyroid can be misinterpreted as a parathyroid adenoma. Hashimoto's thyroiditis or Graves' disease goiters are associated with imaged lymph nodes that can be confused with parathyroid adenomas. Calcifications within the thyroid or a thyroid nodule, cartilage or air within the edge of the trachea or larynx, and the sternoclavicular bone preclude imaging parathyroid glands located posterior to these structures. As a general rule, if an abnormal parathyroid gland cannot be seen with ultrasound, it is presumptive evidence that the abnormal parathyroid gland is more likely to be a superior parathyroid adenoma, because of the natural difficulty in imaging these glands with ultrasound. When an ectopic parathyroid adenoma can be seen with ultrasound, the surgical approach is much simpler than in the preimaging era when a standard bilateral cervical exploration was planned to locate the parathyroid adenoma in a patient with primary hyperparathyroidism. As reported by other investigators, it is the author's preference to forego any other imaging technique for locating abnormal parathyroid glands once the offending parathyroid is precisely identified with ultrasound [36].

Parathyroid Scan

Another very useful localization study is the parathyroid nuclear medicine scan [37]. Technetium sestamibi will be concentrated in any anatomic structure with increased mitochondria, which includes the thyroid gland and abnormal parathyroid glands. The parathyroid adenoma will hold on to the technetium sestamibi longer than the thyroid gland. This fact allows comparing the initial post-injection parathyroid scan with subsequent images taken 2–3 h later to undercover the location of the parathyroid adenoma. Another useful technique for parathyroid scanning is to obtain subtraction imaging. The patient is initially given technetium pertechnitate, which gets picked up by the thyroid gland and not abnormal parathyroid glands. This is followed by an injection of perchlorate, which washes the technetium pertechnitate out of the thyroid gland. Finally, an injection of technetium sestamibi is given. The patient must remain still between images taken after the two technetium injections. The computer can then subtract the first image from the second image to locate the abnormal parathyroid gland. Delayed imaging can be obtained with this technique as well. More precise localization is achieved by adding fused CT scan imaging or SPECT (single photon emission computed tomography) imaging [38]. This gives a three dimensional localization to planar discordant imaging [39]. Besides locating the abnormal gland, parathyroid scanning can alert the surgeon to the presence of an ectopic location.

One study on the technique concluded that combined SPECT/CT scanning produced more reliable localization of ectopic parathyroid adenomas [40]. This is particularly useful for identifying the mediastinal parathyroid adenoma (see Fig. 25.4). Such knowledge can direct further

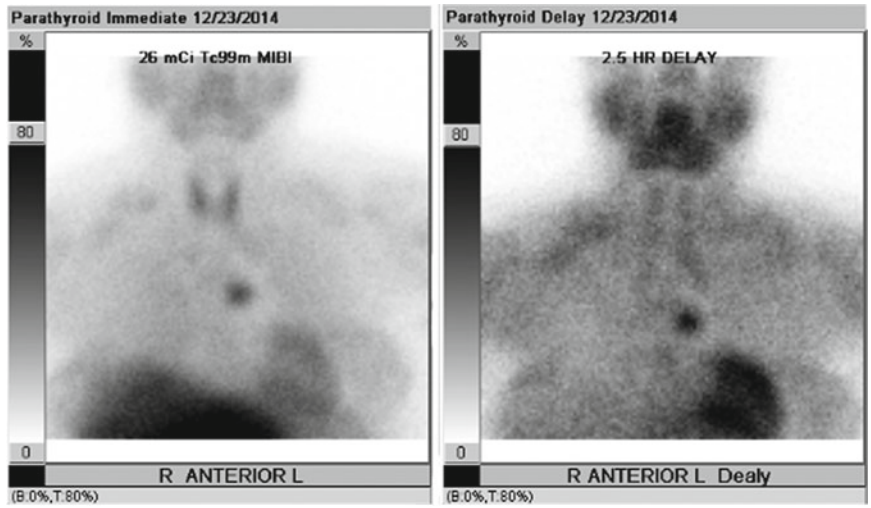

Fig. 25.4 Mediastinal parathyroid adenoma on technetium sestamibi scan

diagnostic investigation of a suspected mediastinal parathyroid adenoma and obviate the need for a central neck parathyroid exploration. Undescended parathyroid adenomas are a little more difficult to discern, because of adjacent uptake of technetium sestamibi by salivary glands. Parathyroid sestamibi scans are successful in localizing approximately 70–80 % of parathyroid adenomas. Difficulties in localization of the abnormal parathyroid gland particularly arise with small adenomas and parathyroid hyperplasia [39]. A study of 185 patients operated on for hyperparathyroidism, of which 19 % had ectopic parathyroid glands, found a significant positive correlation between adenoma weight and positive imaging studies. An ectopic parathyroid location, however, did not correlate with a negative imaging study [41].

There have been incidental reports of positron emission tomography (PET) computed tomography scanning with [18]fluorodeoxyglucose (FDG) identifying ectopic mediastinal parathyroid lesions. The images were initially misinterpreted as identifying metastatic cancer [42, 43].

Cross-Sectional Imaging

A newer useful imaging study for localizing parathyroid adenomas is 4D CT scan imaging [44]. The 4th dimension added to CT scanning is time. Rapid CT scanning is obtained to compare baseline images of the neck and chest with arterial phase images and venous phase images. The parathyroid adenoma has a rich blood supply that creates a localized arterial blush and venous retention that allows separating parathyroid adenomas from lymphadenopathy. If the parathyroid adenoma is immediately adjacent to the thyroid gland then it is more difficult to separate out the abnormal parathyroid gland from the vascular thyroid gland. However, the 4D CT scanning is very useful when the parathyroid adenoma is anatomically separated from the thyroid gland. The CT imaging aids the surgeon in the precise location of the abnormal parathyroid gland and is particularly useful in identifying an ectopic location for a parathyroid adenoma, especially when other imaging modalities are negative (see Fig. 25.5) [45].

The best algorithm for parathyroid imaging is evolving. Ultrasound imaging has no ionizing radiation and can be very accurate in the hands of an experienced and dedicated parathyroid Radiologist. The advent of accurate office imaging of the neck with surgeon performed ultrasound makes this the first approach of choice for many endocrine surgeons, the author included. Additional information concerning thyroid pathology is obtained that can direct further evaluation with ultrasound-

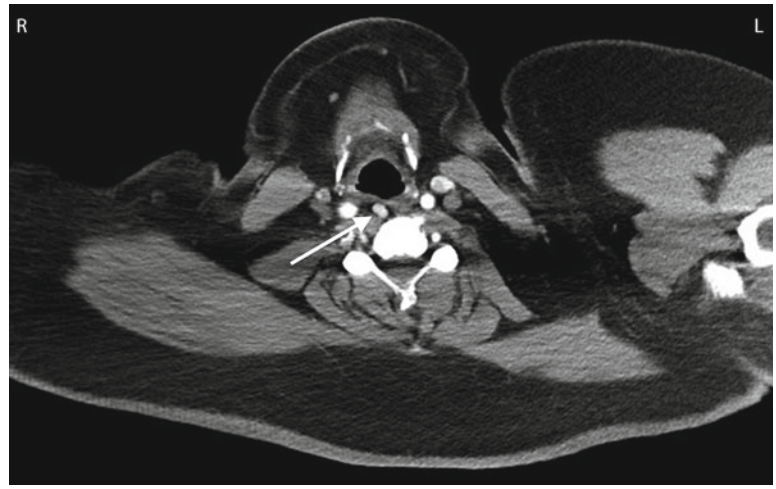

Fig. 25.5 Undescended right superior parathyroid adenoma on 4D CT scan

guided FNA and ultimately preoperative planning. It can be useful to reimage the patient with ultrasound on the operating table to affirm the abnormal parathyroid localization prior to starting the operation. A clearly positive ultrasound exam may be all that is necessary before proceeding with a minimally invasive parathyroidectomy operation. Parathyroid scanning with technetium sestamibi is typically the most useful imaging study following ultrasound. If both ultrasound and nuclear medicine scanning are negative, then 4D CT scanning can be obtained [45]. The role for 4D CT scanning is evolving into a primary modality of parathyroid imaging at some institutions, displacing nuclear medicine studies [46].

The present day imaging techniques for hyperparathyroidism have the distinct advantage of localizing an ectopic parathyroid gland preoperatively. This ultimately can save a lot of operative time and frustration looking for a missing parathyroid gland. It can then direct a minimally invasive operative approach even for an ectopic parathyroid adenoma when combined with intraoperative parathyroid hormone monitoring [47]. The failed operative exploration calls into play the next level of imaging studies, which involve invasive radiologic techniques: arteriography and venous sampling.

Invasive Vascular Imaging

Angiography done with conventional techniques demonstrates a blush of enhancement after contrast injection. This would necessitate selective arterial injections in bilateral internal thoracic, common carotid, inferior thyroid, and superior thyroid arteries [48]. Digital subtraction angiography has been found superior to conventional arteriography by some institutions [49]. Immediately following the arteriographic contrast injection, the arterial vessel is injected with a hypocalcemic stimulating agent (sodium citrate) and then venous blood samples obtained from a catheter in the superior vena cava looking for at least a 1.4 times step-up in the PTH level as a confirmation of the localization [50]. The National Institute of Health has found this localizing technique their invasive imaging procedure of choice with 92 % positive predictive feedback for the combined digital subtraction angiography and arterial stimulation venous sampling. The arterial stimulation venous sampling was less helpful than the digital subtraction angiography [50]. Invasive arterial imaging in the head and neck region, however, carries the rare risk of inducing embolism and stroke that must be discussed with the patient before proceeding with this imaging modality.

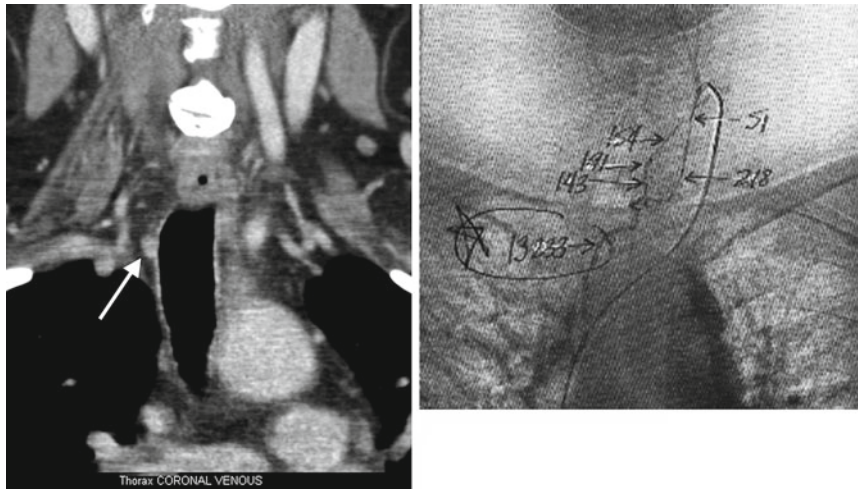

Fig. 25.6 Persistent primary hyperparathyroidism after failed parathyroid exploration

Selective venous sampling for PTH is another useful invasive imaging technique that does not carry the risk of arterial embolization. The primary head and neck venous drainage is mapped out and multilevel venous samples drawn for PTH bilaterally down into the superior vena cava. Selective venous drainage tributaries are also sampled for PTH. Each sample level must be carefully marked on the venous contrast image, and the final PTH levels used to reconstruct the anatomy for PTH, pinpointing a significant step-up point in the PTH of at least twice the baseline elevated PTH [51]. Commonly the step-up PTH is much higher than twice normal (see Fig. 25.6). The technique is very time consuming and requires an experienced interventional radiologist to conduct the study, which may involve as many as 50 selective venous blood samples. Venous drainage PTH levels do not give the same precise localization image of an identified contrast blush within an adenoma as with angiography, but can be very helpful to direct the operative approach to the ectopic parathyroid adenoma or subsequent arteriographic imaging [50, 52]. In general, a missing abnormal parathyroid gland requires two confirming localization imaging studies to direct reoperation with confidence of finding the abnormal parathyroid gland. A positive parathyroid sestamibi scan and a positive 4D CT scan may be all that is necessary to localize a mediastinal ectopic parathyroid adenoma. Frequently, however, one of these imaging studies is negative and invasive imaging studies may be required to further confirm the localization of an ectopic parathyroid adenoma. This is particularly true for ectopic parathyroids within the mediastinum. In some cases a positive invasive imaging study prompts reassessment of the interpretation of images obtained with noninvasive imaging to reestablish the localization of the ectopic parathyroid adenoma.

Operative Approach to Ectopic Parathyroid Adenomas

There are three anatomic levels of operative approach to the ectopic abnormal parathyroid:

1. Upper neck cranial to the thyroid notch that contains an undescended parathyroid gland.
2. Central neck from the thyroid notch to visible superior mediastinum that can be assessed with the standard collar incision for parathyroid exploration.
3. Mediastinum caudal to the usual visualized level from a standard cervical exploration.

It is helpful to address the operative approach to each of these levels separately, following the embryologic descent of the parathyroid glands.

Undescended Ectopic Parathyroid

Either the inferior parathyroid gland (3rd pharyngeal pouch) or the superior parathyroid gland (4th pharyngeal pouch) can be responsible for an undescended ectopic parathyroid [33]. A 31-year study of 1750 patients with renal hyperparathyroidism revealed a 0.91 % incidence (16 patients) of undescended parathyroid. The ratio of undescended inferior to superior parathyroid glands was 3 to 1 [53]. The location in the upper neck is slightly different for each of these glands. Since the inferior parathyroid gland descends with the thymus gland, the undescended complex has been termed the "parathymus." [54] The presence of thymus tissue in the upper neck associated with an ectopic parathyroid gland is the anatomic clue that this represents an ectopic inferior parathyroid gland. The inferior parathyroid can rarely be totally undescended and be as high in the neck as near the angle of the jaw at the level of the hyoid bone. In this location imaging studies will confuse it with submandibular lymph nodes on ultrasound and submandibular salivary glands on parathyroid sestamibi scans. More commonly, the undescended inferior parathyroid gland is found adjacent to the carotid artery at the level of the bifurcation [33]. It is typically anterior/medial to the carotid artery and in this location can be distinguished on the initial neck ultrasound examination from lymph nodes that are typically lateral to the internal jugular vein or medial to the internal jugular vein, but lateral to the carotid artery (see Figs. 25.3 and 25.7). A hypoechoic nodular structure on ultrasound medial to the carotid artery in the setting of primary hyperparathyroidism should be considered an undescended parathyroid adenoma until proven otherwise. It is rare, however possible, to have an ectopic parathyroid adenoma lateral to the carotid artery [55, 56].

The superior parathyroid gland when undescended can be typically found medial/posterior to the common carotid artery just below the bifurcation [57]. In this position it can sometimes be imaged with ultrasound. The undescended superior parathyroid gland can also be found posterior to the upper larynx/pharynx and in this position the adenoma requires 4D CT scan imaging for an accurate localization (see Fig. 25.5). If the superior parathyroid primordium fails to separate from the remaining endoderm of the 4th pharyngeal pouch, it may migrate to a retropharyngeal location with the pyriform sinus primordium [58]. This can lead to an undescended parathyroid adenoma within the pyriform sinus that can be visualized on a laryngoscopic examination as a unilateral superficial bulging of the pyriform sinus. In this rare case, the parathyroidectomy approach can be conducted via laryngoscopy, ideally using endoscopic CO_2 laser resection [59]. A very rare location for an undescended parathyroid is within the vagus nerve or even hypoglossal nerve [60, 61]. Tissue between the 3rd and 4th pharyngeal pouches contributes to these nerves and can therefore have elements of parathyroid tissue within the nerve that may ultimately develop into a parathyroid adenoma. Vocal cord paralysis has been reported as a presenting sign of intravagal ectopic parathyroid adenoma [62].

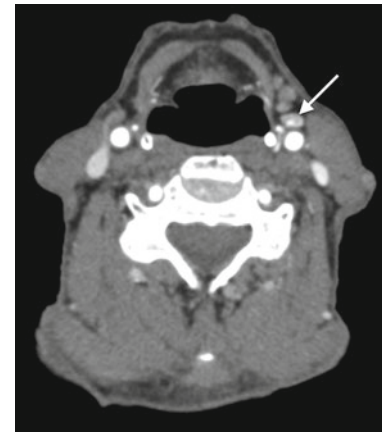

Fig. 25.7 Undescended left inferior parathyroid adenoma

The surgical approach to the typical undescended parathyroid gland requires precise localization with imaging studies, usually ultrasound and/or a 4D CT scan (see Figs. 25.4, 25.5, and 25.7). The localization is preferably confirmed with directed fine needle aspiration for PTH, usually done with ultrasound guidance [63]. For the

parathyroid glands not amenable to ultrasound-guided FNA, elevated internal jugular venous PTH samples will confirm the ectopic imaged location in the upper neck [34]. A precise localization with a 4D CT scan can be enough to direct surgery in the classic clinical setting of primary hyperparathyroidism (see Figs. 25.5 and 25.8).

Depending on the patient's anatomy and the location of the ectopic undescended parathyroid adenoma, surgery can be done under local anesthesia through a field block combined with intravenous sedation (Monitored Anesthesia Care). Otherwise, general anesthesia can be used with the optional use of intraoperative nerve monitoring for testing the vagus nerve during surgical exposure. If the undescended parathyroid adenoma can be imaged with ultrasound, then the ultrasound examination can be repeated in the operating room once the patient is positioned for surgery for planning the operative incision. If the parathyroid can't be imaged with ultrasound, the relative location to the bifurcation of the carotid artery and hyoid bone can be noted for reference in planning the location of the incision. Generally a transverse incision is made in the upper medial neck on the side of the tumor following a natural skin line (see Figs. 25.4, 25.7, and 25.9). The incision is extended in the deeper anterior neck to mobilize the sternohyoid muscle medially and the sternocleidomastoid muscle laterally to

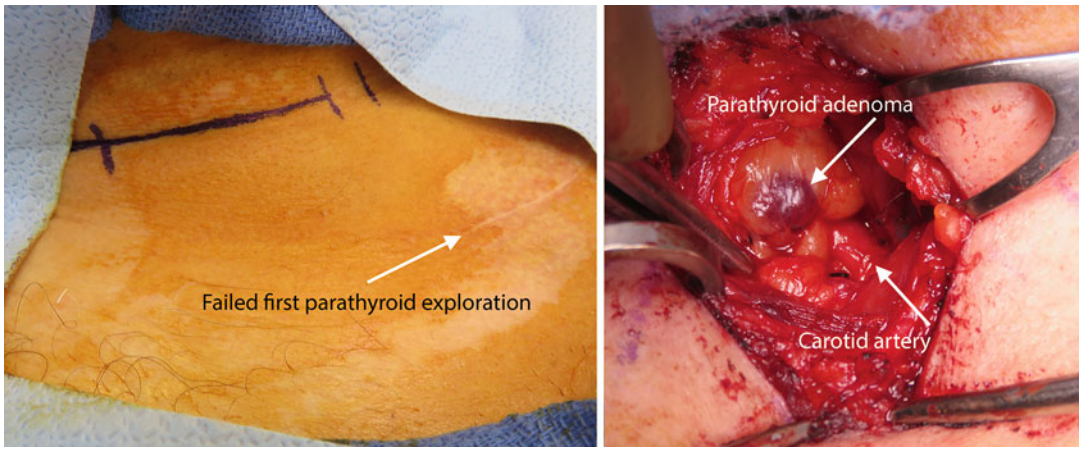

Fig. 25.8 Undescended right superior parathyroidectomy

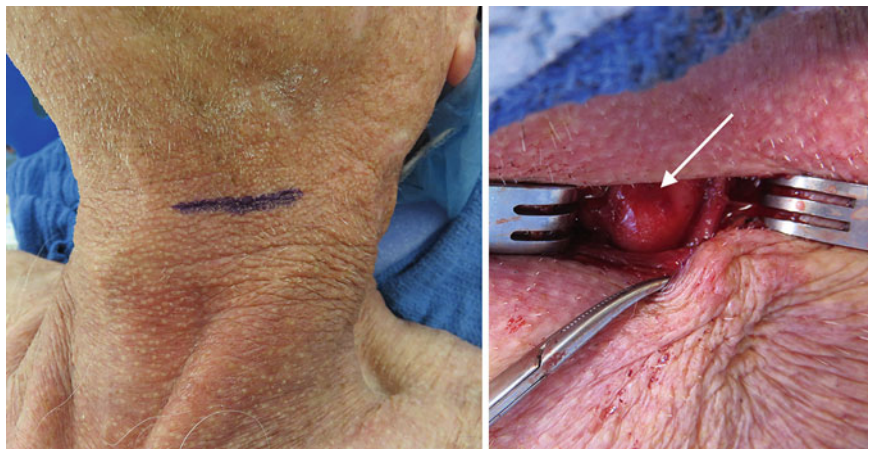

Fig. 25.9 Undescended left inferior parathyroidectomy

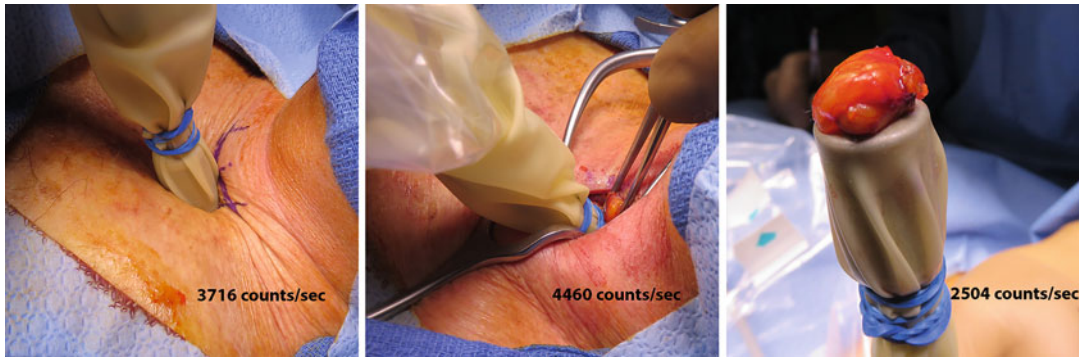

Fig. 25.10 Gamma probe localization of a left superior parathyroid adenoma

expose the underlying carotid artery. An adjunct to guide dissection and identification of the abnormal parathyroid gland that the author has found useful is to inject the patient with technetium sestamibi approximately 2–3 h prior to the start of the surgery to allow use of a gamma probe to locate the abnormal parathyroid gland (see Fig. 25.10). This technique is useful even if the parathyroid sestamibi scan was negative preoperatively. A skin gamma radioactive count in counts/second (with or without a columnator, the author prefers without) is obtained before the incision and the gamma probe used to direct deeper dissection once the carotid artery area is exposed. The closer the dissection gets to the parathyroid adenoma the higher the radioactive counts become. Once the parathyroid adenoma has been excised, the ex-vivo radioactive counts can be taken to confirm that an offending parathyroid gland has been removed. The surgery is similarly combined with intraoperative PTH monitoring to insure that only one abnormal parathyroid gland exists [64]. With this approach frozen section confirmation of a parathyroid adenoma is not usually necessary.

Central Neck Ectopic Parathyroid

The standard cervical collar incision close to the isthmus of the thyroid can generally be used to identify and excise an ectopic abnormal parathyroid gland between the thyroid notch of the larynx down to the upper superior mediastinum. A precise localization of the abnormal parathyroid gland preoperatively is extremely helpful in planning surgical dissection and allowing a minimally invasive parathyroidectomy approach. This may allow a laterally placed transverse incision to approach the central neck by medially displacing the lateral edge of the strap muscles along the medial edge of the sternocleidomastoid muscle [44]. The author prefers to continue with the transverse central neck incision even in reoperative cases since this gives the greatest flexibility to dissect both sides of the central neck if operative findings dictate that approach, as when the intraoperative PTH levels do not drop sufficiently to indicate only unilateral disease. Use of the gamma probe following injection of the patient 2–3 h preoperatively with technetium sestamibi can be helpful in directing deeper dissection for a posteriorly displaced parathyroid adenoma. Prior to the central neck incision, four quadrant skin radioactive counts can be recorded form the general area of the normal anatomic location of the four parathyroid glands (right inferior and superior, left inferior and superior). These radioactive counts can be used as a reference to guide deeper dissection, since the radioactive counts will increase the closer the gamma probe gets to the abnormal parathyroid gland. Once the parathyroid gland is excised, ex-vivo radioactive counts over in-vivo radioactive counts of at least 20 % can be used to readily confirm that the abnormal parathyroid gland had been discovered and removed (see Fig. 25.10). This technique will be most helpful in an ectopic parathyroid adenoma

localized on a parathyroid sestamibi scan. The author, however, has also found it useful even in patients with a negative preoperative localization study using technetium sestamibi (unpublished results). A significant drop of the intraoperative PTH levels can also be used to confirm uniglandular parathyroid disease that allows for minimally invasive parathyroidectomy surgery [64]. Intraoperative PTH monitoring is equally effective for surgical management of hyperfunctioning ectopic parathyroid glands. An evaluation of surgical results in 1195 patients undergoing parathyroidectomy for sporadic primary hyperparathyroidism found 120 patients (10 %) had hyperfunctioning ectopic glands. There was an overall 93 % operative success for these patients using a combination of preoperative localization studies and intraoperative PTH monitoring [65].

Patients with nonlocalizing imaging studies preoperatively for primary hyperparathyroidism or an inadequate drop of the intraoperative PTH levels following excision of the preoperatively localized abnormal parathyroid gland pose a different problem to the endocrine surgeon. This frequently requires a 4 gland exploration looking for 1 or more abnormal parathyroid glands. Previous studies on reoperative surgery for persistent primary hyperparathyroidism prior to the advent of current parathyroid imaging techniques demonstrated that the majority of missed parathyroid adenomas were still in the central neck compartment and could be reached through the initial parathyroid exploration incision [50, 66, 67]. In the hands of an experienced endocrine surgeon this occurrence can be minimized by a systematic operative approach to uncover the abnormal ectopic parathyroid gland. The search for an ectopic parathyroid gland is aided by knowledge of whether the missing parathyroid gland is suspected to be an inferior or superior parathyroid gland. This is sometimes difficult to precisely determine intraoperatively. The presence of thymus gland with the parathyroid gland is a tip-off that the identified parathyroid gland, irrespective of the location, is an inferior parathyroid gland. Searching for symmetrical parathyroid locations is also helpful, but sometimes the missing parathyroid is not easy to locate.

The missing inferior parathyroid gland requires looking first in the thyrothymic ligament down to and including the cervical extension of the thymus gland all the way to as much of the superior mediastinal portion of the thymus gland that can be retracted into the neck [68]. A negative localization then requires searching the deeper paratracheal and paraesophageal tissues from above the superior pole of the thyroid to the thoracic inlet. The weight of an enlarged inferior parathyroid gland can displace it posteriorly all along the path of embryologic descent. Sometimes, a more superiorly identified parathyroid gland reveals that the initial localized parathyroid gland lateral to the mid-thyroid was not in fact the superior parathyroid gland, but the inferior parathyroid gland. Intraoperative nerve monitoring using electrode imbedded endotracheal tubes can be very helpful in identifying the course of the recurrent laryngeal nerve for preservation while exposing the deeper paratracheal and paraesophageal tissues [69]. A negative localization then requires searching the carotid sheath from the thoracic inlet to superior to the thyroid. The missing parathyroid gland can be posterior to the carotid artery [70].

With a continued negative exploration, a missing inferior parathyroid gland could possibly be an intrathyroidal parathyroid adenoma [27, 28]. In this case the preoperative ultrasound assessment of the thyroid is extremely helpful in determining whether thyroid lobectomy is indicated. A normal thyroid ultrasound precludes any need for thyroid lobectomy. It's helpful to know the size and location of the ultrasound identified thyroid nodules to determine whether there is a possibility of an intrathyroidal parathyroid adenoma. Intraoperative ultrasound may be helpful at this point. Typically, the intrathyroidal parathyroid adenoma is subcapsular and can be readily unroofed. If a true intrathyroidal parathyroid adenoma is suspected representing a missing inferior parathyroid, usually a partial thyroidectomy of the lower half of the thyroid lobe is sufficient to exclude this possibility, but only if there are thyroid nodules suspicious for a missing adenoma [32]. A clearly suspicious thyroid nodule for an intrathyroidal parathyroid adenoma can be

approached through a thyroidotomy and enucleation of the nodule.

The missing superior parathyroid gland requires a complete mobilization of the superior pole of the thyroid lobe to insure that an ectopic parathyroid gland posterior to the tip of the superior pole of the thyroid or above the superior tip of the thyroid lobe is not overlooked. Sometimes a superior parathyroid gland in a normal location requires complete mobilization of the superior pole to uncover the location of the parathyroid gland. With negative exploration after mobilization of the superior pole of the thyroid, the deeper paratracheal and paraesophageal tissues must be dissected all the way down into the superior posterior mediastinum [14]. The superior parathyroid adenoma can lie even posterior to the trachea or esophagus. This exposure is similar to looking for a missing inferior parathyroid adenoma.

A common ectopic displacement of a superior parathyroid adenoma is to the deep paratracheal and paraesophageal tissues posterior or caudal to the inferior pole of the thyroid and sometimes even down into the superior posterior mediastinum (see Fig. 25.11). The carotid sheath needs to be explored if dissection continues to be unsuccessful for localization of the missing superior parathyroid gland. A truly intrathyroidal superior parathyroid adenoma is very unusual, but possible. The same assessment of the thyroid with ultrasound is essential to revealing the location of a possible intrathyroidal superior parathyroid adenoma. In the author's experience this rare occurrence is usually within the posterior midportion of the thyroid and can be approached sometimes through a thyroidotomy and enucleation of the nodule so as to avoid a thyroid lobectomy.

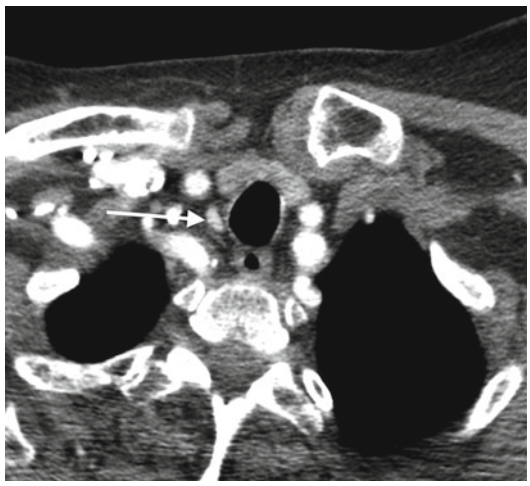

Fig. 25.11 Paratracheal right superior parathyroid adenoma

Exploration for a missing ectopic parathyroid adenoma can be aided by gamma probe localization following the injection of technetium sestamibi prior to the operation. The author has found this very useful on a number of occasions. It does not require a positive preoperative sestamibi scan to be useful, since most parathyroid adenomas do take up technetium sestamibi. The intraoperative gamma probe is more sensitive than the parathyroid imaging study. The timing of the exploration after the injection is not critical. The author has found it useful even up to 6 h following the injection of technetium sestamibi. The reason for this is that gamma probe radioactive counts used to aid dissection are all relative to the location of where the counts are taken (skin versus parathyroid adenoma) at the time of surgical exploration. Radioactive counts are obtained from the skin level using the gamma probe and recorded in the four usual quadrants of the thyroid. Then with deeper central neck exploration the ectopic parathyroid adenoma can be suspected when increasing radioactive counts are detected above the skin level and gradually higher radioactive counts as the gamma probe gets closer to the parathyroid adenoma. The gamma probe is very specific in the directional indication of the location of an ectopic parathyroid adenoma, thus aiding the surgeon as to where to look for the missing ectopic parathyroid gland. Unfortunately, some parathyroid adenomas weakly concentrate technetium sestamibi, depending of the degree of increased mitochondria within the parathyroid adenoma and oxyphil versus chief cell component, so that gamma probe localization is not helpful. Small parathyroid adenomas also become more difficult to localize with the gamma probe. Even so, generally nothing is lost in trying to use gamma probe localization for difficult intraoperative parathyroid adenoma localization and identification.

If a thorough central neck exploration for a missing ectopic parathyroid adenoma is performed as described and remains negative, then the location is presumed to be undescended or mediastinal. The undescended location can be suspected by taking bilateral internal jugular venous blood samples for PTH and detecting a distinct lateralization (two to fourfold ioPTH gradient) [34]. Lee et al. reported using this technique to successfully locate and remove undescended parathyroid adenomas in three patients [71]. Sometimes all four parathyroid glands are identified. In this case supernumerary parathyroid glands can be suspected, assuming the correct clinical diagnosis of hyperparathyroidism has been firmly established. The most common location will be associated with the thymus gland and excision of cervical thymus and as much of the superior mediastinal thymus as can be retracted into the neck is indicated [21]. With a negative exploration for the offending abnormal parathyroid gland, in depth imaging studies for an undescended or mediastinal ectopic parathyroid gland is indicated. The author prefers to wait for 3 months to allow complete healing of the initial cervical exploration, before undertaking extensive imaging studies for the missing ectopic parathyroid gland.

Mediastinal Ectopic Parathyroid

Parathyroidectomy for a mediastinal parathyroid adenoma depends on a precise localization before proceeding with surgical excision. A blind mediastinal exploration for a suspected mediastinal parathyroid adenoma as occurred for Captain Martell in the 1920s is rarely ever indicated. A number of surgical options are available to the endocrine surgeon for excision of a mediastinal parathyroid adenoma. These include the standard median sternotomy (partial [72] or complete) and thoracotomy, but also less invasive procedures like a cervical reexploration using sternal lift devices or mediastinoscopy and video-assisted thorascoscopy (VATS) [73]. Frequently, excision of a mediastinal parathyroid requires the combined expertise of an endocrine surgeon and thoracic or cardiac surgeon, depending on the location of the ectopic parathyroid and surgical approach. Iacobone et al. completed a comparative study of various surgical approaches to mediastinal parathyroid tumors in 63 patients. The study included mediastinal exploration by a conventional cervicotomy, video-assisted approaches (thoracoscopy and transcervical mediastinoscopy) and sternotomy. No complications occurred after video-assisted parathyroidectomy, while an overall morbidity rate of 50 % and 10 % was found after sternotomy and conventional cervicotomy approaches respectively. Postoperative pain and hospital stay were significantly increased following sternotomy. The patient's subjective cosmetic satisfaction was significantly higher after video-assited and conventional cervicotomy approaches [74].

The choice of operative approach is aided by precise localization preoperatively, which can then lead to an initial one-gland exploration for mediastinal parathyroid adenoma [75]. Two endoscopic approaches to confirming the diagnosis and location of a suspected ectopic mediastinal parathyroid adenoma are endobronchial and transesophageal FNA [76, 77]. Using a bronchoscope or upper GI endoscope with endoscopic ultrasound, a nodular structure adjacent to either the esophagus or trachea can be imaged and fine needle aspirates obtained for cytology and PTH measurement as described earlier for ultrasound parathyroid imaging. Intraoperative PTH combined with the initially planned one-gland mediastinal parathyroidectomy proved to be useful in a 10-year study by Sagan and Gozdziuk in identifying patients that additionally needed a cervical parathyroid exploration for multiglandular disease. A potential 21 % operative failure was reduced to 3 % with the use of ioPTH [78].

Ectopic parathyroid in the mediastinum can be separated into superior mediastinum, anterior or posterior, and mid-mediastinum, anterior or posterior. The latter includes rare locations in the aortopulmonary window, along the aortic arch, and pericardium.

Superior Mediastinal Ectopic Parathyroid

Since the inferior parathyroid gland is the most likely parathyroid gland to be ectopic in the mediastinum, the majority of ectopic mediastinal parathyroid adenomas are going to be in the superior mediastinum with an intrathymic location [74, 79]. Most of these ectopic parathyroid glands will therefore be in the anterior mediastinum and can be approached with a cervical incision as demonstrated in Fig. 25.12 for this morbidly obese patient (BMI 50), prepped for possible sternotomy. Removing the superior mediastinal parathyroid adenoma through a directed cervical incision can make the difference between doing an outpatient parathyroidectomy or a sternotomy for parathyroidectomy that leads to several days of hospitalization and prolonged recovery. There are lift devices like the Rultract Skyhook Retractor that can be applied to the sternum to increase the degree of exposure of the upper mediastinum if necessary (see Fig. 25.13) [73, 80]. Just an extra 2 cm of anterior-posterior exposure can make a big difference when trying to visualize the thymus gland. It can be gradually retracted up into the neck with gentle grasping of the fatty thymic tissue and sequential ligation of feeding veins while increasing more and more the retraction of the thymus gland. An alternative approach is to use mediastinoscopy through the cervical incision to localize the intrathymic parathyroid adenoma

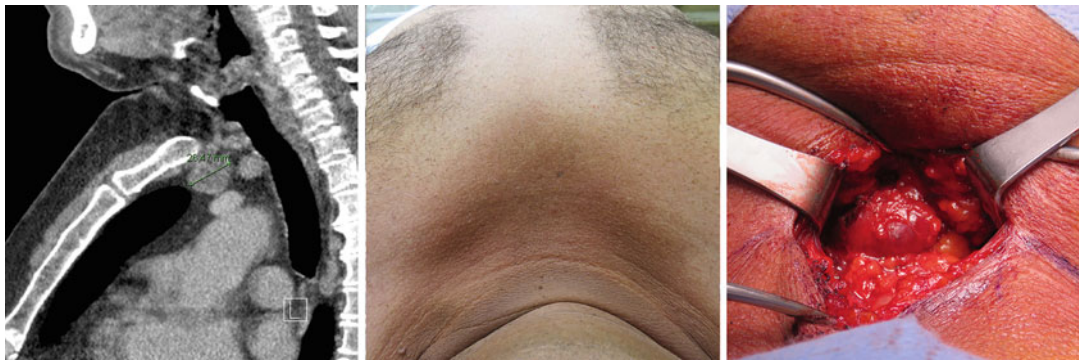

Fig. 25.12 Superior mediastinal right inferior parathyroidectomy through a cervical incision

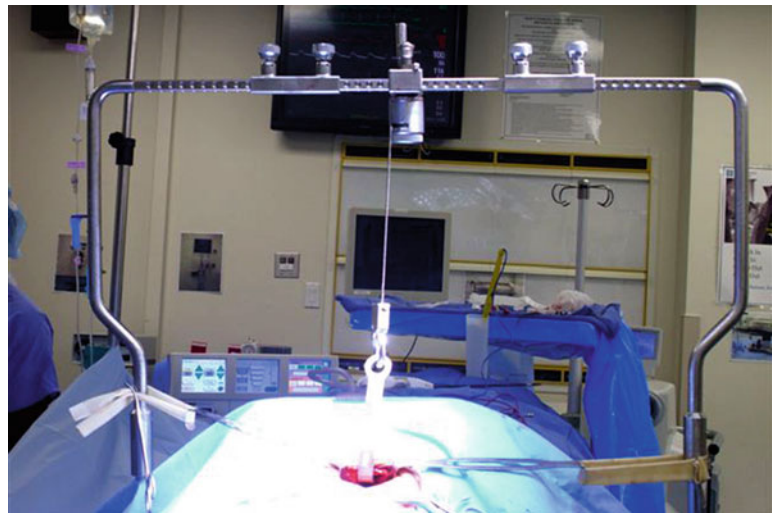

Fig. 25.13 Sternal lift device for cervical incision approach to a mediastinal parathryroid

and direct excision of the parathyroid [81–83]. The fallback technique will always be a traditional median sternotomy, partial or complete, but this should rarely be necessary for upper anterior mediastinal parathyroid glands [84]. Gamma probe localization can be used to confirm excision of the imaged parathyroid adenoma on a technetium sestamibi scan, but it is well to remember that the heart takes up technetium sestamibi as well and can interfere with directing the localization of the abnormal mediastinal parathyroid gland from a cervical approach.

Ectopic parathyroid adenomas in the superior posterior mediastinum are likely to be sizeable posteriorly descended superior parathyroid glands [74]. The unrestricted tissue plane into the posterior mediastinum from the neck more readily allows for descent of a parathyroid adenoma into a location behind the great vessels. Gravity, repetitive swallowing, and the negative intrathoracic pressure aid in promoting this descent into the posterior mediastinum. However, most of these posteriorly descended parathyroid glands can still be reached through a cervical incision, even when in the superior mediastinum [75]. When the location of the posterior mediastinal ectopic parathyroid gland and the patient's body habitus do not allow a cervical approach, alternative thoracic approaches with video-assisted thoracoscopic surgery (VATS) or thoracotomy can be considered [85].

Mid-Mediastinal Ectopic Parathyroid

The location of a parathyroid adenoma in the mid-mediastinum presents different challenges for access to excise the parathyroid gland [86]. The assistance of a thoracic surgeon is frequently necessary. Ectopic anterior mediastinal parathyroid adenomas in the lower thymus, aortopulmonary window between the aortic arch and bifurcation of the pulmonary artery [87], along the aortic arch or pericardium [88] can be readily exposed with a median sternotomy (see Figs. 25.14 and 25.15). The postoperative morbidity, delayed recovery, and increased hospital stay of a median sternotomy have promoted alternate more minimally invasive techniques to excise the ectopic parathyroid gland. A 30-year review of mediastinal parathyroidectomy in 33 patients at the Mayo Clinic demonstrated a significantly shorter length of hospital stay and less morbidity with minimally invasive mediastinal parathyroidectomy compared to open surgery [89]. VATS approaches through either the right or left chest or video-assisted mediastinoscopy through the neck have been demonstrated to reduce morbidity and enhance recovery from the operation [75, 82, 90]. The possibility of even outpatient VATS for mediastinal parathyroid adenoma has been reported [91]. An alternate minimally invasive technique to consider for mediastinal parathyroidectomy with the proper

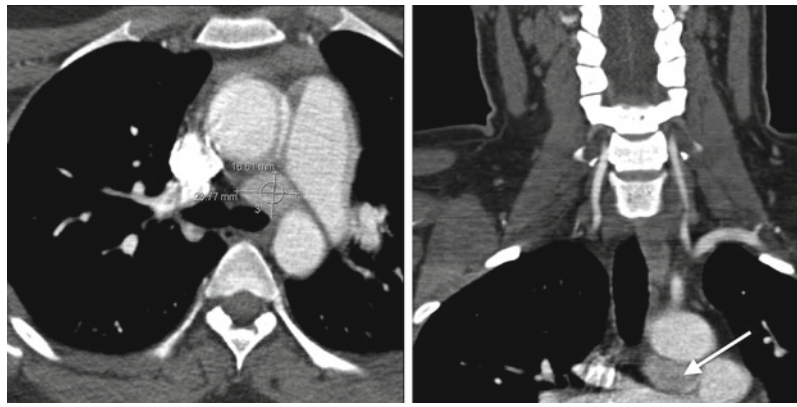

Fig. 25.14 Aortopulmonary window parathyroid adenoma on 4D CT imaging (axial and coronal)

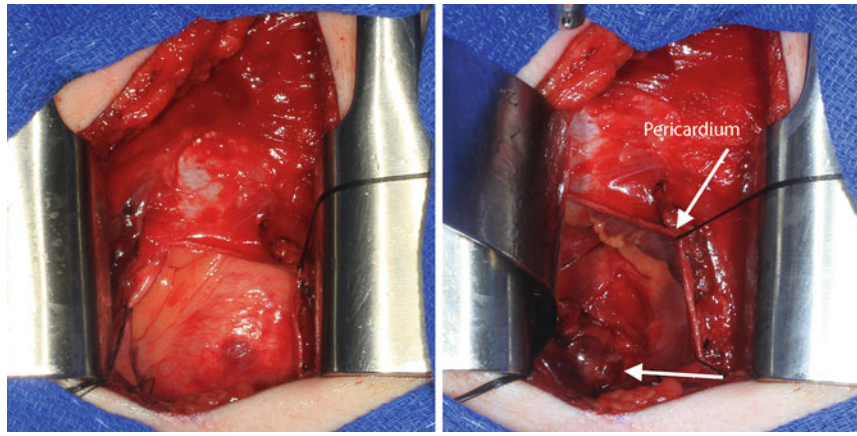

Fig. 25.15 Aortopulmonary window parathryoid adenoma

anatomic localization is parasternal videomediastinoscopy [92].

The precise localization of the ectopic mediastinal parathyroid adenoma is critical to planning VATS surgery [93]. Experience with video-assisted approaches at Duke in 17 patients showed a 100 % cure rate in patients with two or more concordant studies locating parathyroid tissue in the mediastinum and 60 % cure rate in those with one positive study [56]. It is well to remember that other mediastinal neoplastic abnormalities, such as thymoma, can give a false positive localization of a suspected mediastinal parathyroid adenoma on technetium sestamibi scanning [90]. The video-assisted approach is most useful for ectopic parathyroid adenomas deep in the anterior or posterior mid-mediastinum. The fallback approach for the posterior mid-mediastinum is a thoracotomy, which carries similar drawbacks to a median sternotomy [85].

Gamma probe localization of mediastinal parathyroid adenomas has been demonstrated to aid excision of ectopic parathyroids through the open and video-assisted approaches [94–96]. Another dissection aid reported to optimize thoracoscopic resection of mediastinal parathyroid adenomas is the injection of methylene blue 4 mg/kg intravenously before exploring the mediastinum [97]. The abnormal parathyroid gland will concentrate the dye to enhance visual identification of the parathyroid adenoma within a fatty casing. Robotic technology appears to be a promising adjunct to VATS to facilitate the utilization of this approach for excision of ectopic parathyroid adenomas in the mediastinum (see Fig. 25.16) [88, 98, 99]. Nonoperative approaches to definitive treatment of mediastinal parathyroid adenomas have emerged that appear particularly useful for difficult to reach abnormal parathyroids, such as in the aortopulmonary window. The primary arterial blood supply to the aortopulmonary window parathyroid adenoma arises from the bronchial artery. This lends itself to transcatheter emolization for successful correction of hyperparathyroidism from the ectopic parathyroid [100, 101].

Summary

The parathyroid surgeon needs to be well versed in the embryologic formation and descent of the separate inferior and superior parathyroid glands so as to anticipate common ectopic locations of the abnormal parathyroid gland. Present day localization imaging techniques allow identification of the ectopic parathyroid adenoma preoperatively before the first parathyroid operation, thus allowing a minimally invasive approach guided by intraoperative PTH monitoring and gamma probe localization. In cases of an undescended upper neck parathyroid adenoma or a mediastinal parathyroid adenoma, the need for a central neck exploration can be eliminated. A systematic surgical approach to localization of a missing ectopic parathyroid gland in

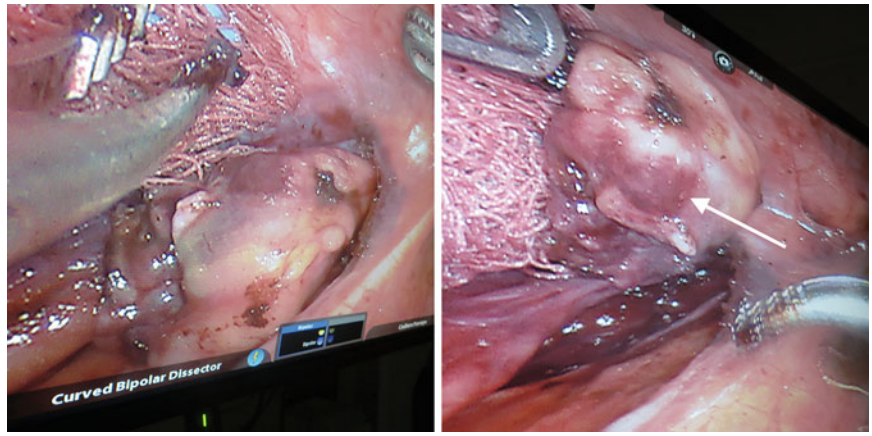

Fig. 25.16 Robotic VATS excision of ectopic left inferior intrathymic parathryoid adenoma

the central neck can drastically reduce the occurrence of a failed identification of the abnormal parathyroid with the initial parathyroidectomy operation. Ectopic parathyroid adenomas in the mediastinum can frequently be approached surgically with less invasive techniques to obviate the need for a more debilitating median sternotomy or thoracotomy.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion

The expert parathyroid surgeon needs:

- In-depth understanding of fetal migration pathways for inferior and superior parathyroid glands.
- Optimal use of preoperative localization studies that may identify ectopic parathyroid glands.
- Operative management in the central neck looking for the missing, possible ectopic parathyroid.
- Optimal localization studies to aid in localizing the missing abnormal parathyroid gland.
- Operative techniques to direct excision of undescended or mediastinal abnormal parathyroid.

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Robotic Parathyroidectomy

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Salem I. Noureldine, Fadi Murad, Emad Kandil, and Ralph P. Tufano

Contents

Summary Points

- The da Vinci Surgical Robot System is considered to be the latest addition to the endocrine surgeon's armamentarium to accomplish remote-access, targeted parathyroidectomy.
- This novel tool restores some of the fundamentals of the surgical technique that were lost in conventional endoscopic surgery, making it particularly advantageous in the restricted workspace afforded in this region of the body.
- Robotic parathyroidectomy avoids a cervical scar by concealing the incision in the axilla, infraclavicular area, or the retroauricular area. Mediastinal parathyroidectomy using the da Vinci robot is achieved through the intercostal space, depending on adenoma localization.
- Robotic parathyroidectomy represents an appealing option to patients with a tendency for hypertrophic or keloid scarring and those whom the cosmetic impact of a cervical scar has significant social stigma or concern.
- Preliminary results of robotic parathyroidectomy from small case series and case control studies have shown it to be equivalent to the conventional, transcervical targeted parathyroidectomy with regards to cure and complication rates.
- Limitations of robotic parathyroidectomy include its high cost and longer operative time compared to conventional techniques.

Electronic supplementary material: The online version of this chapter (doi:10.1007/978-3-319-26794-4_26) contains supplementary material, which is available to authorized users.

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- Ideal patient selection criteria are not well established and society guidelines are lacking. This particularly relates to the patient's body habitus and the presence, or lack of concordant imaging to localize the parathyroid lesion.
- Long-term prospective randomized control studies with larger sample sizes are needed to identify the role that robotic parathyroidectomy has to play in the management of patients with primary hyperparathyroidism.

Introduction

Historically until the 1990s, a low collar incision involving bilateral cervical exploration of all four parathyroid glands and removal of any that are grossly enlarged had been the standard surgical treatment for primary hyperparathyroidism (PHPT). This approach facilitates a safe dissection and is associated with low morbidity in experienced hands. Yet, some patients are still left with a noticeable cervical scar, most of which are women who are understandably concerned about limiting the cosmetic impact of the cervical incision. As a result, there has been a great desire among both surgeons and patients to minimize cervical incisions. Significant improvements in endoscopic instrumentation, preoperative localization studies, intraoperative adjuncts, and the increased understanding of the endoscopic cervical anatomy have facilitated the further growth of head and neck endoscopic and minimally invasive surgery [1]. The first unilateral approach for solitary parathyroid adenomas was reported by Tibblin et al. [2]. Since then, several targeted techniques have been described, including radioguided parathyroidectomy, endoscopic parathyroidectomy with gas insufflation, and video-assisted parathyroidectomy without gas insufflation [3–5]. These minimally invasive approaches have led to fewer complications, shorter operative time and hospitalization, quicker recovery, and greater patient satisfaction [6]. Minimally invasive, targeted parathyroidectomy is therefore recommended when a parathyroid adenoma is localized preoperatively, as it can be removed without visualizing the other glands, and the rapid intraoperative parathyroid hormone (IOPTH) assay is employed to confirm an adequate resection. Currently, this approach has replaced bilateral neck exploration in patients with localized disease, although a traditional cervical incision with bilateral neck exploration remains the optimal surgery for nonlocalized disease and cases of hyperplasia [4, 7].

Concurrent with these developments, other surgeons experimented with remote access techniques designed to relocate the surgical incisions outside the neck so that they are "invisible" incisions. These techniques emerged primarily in Asian centers, where there is a higher risk of hypertrophic scarring and a cultural emphasis on the cosmetic appearance of the anterior neck. As technology and training advanced, the da Vinci Surgical Robot System (Intuitive Surgical, Sunnyvale, CA, USA) facilitated the ability to perform parathyroid surgery without any visible cervical incisions via a gasless transaxillary approach [7–11]. Surgeons have found that the ability to control a high definition camera system and multiarticulated endoscopic arms through a single console restores some of the fundamentals of the surgical technique that were lost in conventional endoscopic surgery, making it particularly advantageous in the restricted workspace afforded in this region of the body [12–14].

As surgeons in the USA began to implement this approach, concerns emerged over the safety of the technique in patients with a larger body habitus [15–18]. The transaxillary approach also required placement of drains and necessitated hospital admission, which represented a step backwards from advances made in minimally invasive surgery during the prior decade. An alternate robotic remote access approach, the robotic facelift (retroauricular) approach, was recently developed to help overcome the concerns and limitations of the robotic transaxillary approach in the western patient population [19, 20].

To date there are no randomized control trials to assess how these innovative techniques compare to conventional targeted parathyroidectomy. There are only 6 nonrandomized studies that

evaluate robotic parathyroidectomy [7, 9, 11, 21] in the literature, two of which compare robotic parathyroidectomy with targeted, transcervical parathyroidectomy [10, 22].

Indications

It was only during the last two decades that targeted parathyroidectomy was widely established. The development of high-resolution ultrasound (US), sestamibi scintigraphy, and introduction of the rapid IOPTH assay has greatly laid the foundation for minimally invasive and targeted parathyroidectomy [23, 24]. If preoperative localization studies allow for a more targeted approach, the IOPTH assay is able to intraoperatively confirm the success for surgery before the patient leaves the operating table [25].

The diagnosis of PHPT is mostly established by demonstrating hypercalcemia in the setting of an elevated intact PTH level. Familial hypocalciuric hypercalcemia and vitamin D deficiency must be ruled out by measuring the 24-h urine calcium and serum vitamin D levels, as surgery will not be required in these patients. PHPT is most commonly due to a single adenoma. However, approximately 15 % of cases may be a result of multiple gland disease (MGD), either due to 4-gland hyperplasia or double adenomas. While most commonly a sporadic disease, PHPT due to MGD can be part of a familial syndrome in a small subset of patients (5 %). Indications for parathyroidectomy are no different in patients with sporadic or familial PHPT [26, 27]. However, patients with sporadic primary hyperparathyroidism with an adenoma localized by preoperative imaging techniques are candidates for targeted parathyroidectomy.

Patient Selection

Robotic parathyroidectomy takes advantage of the endoscopic magnification that allows performing the same intervention through a remote, so-called scarless access. This is theoretically associated with a lower risk of complications due to optimal 3D visualization of neck structures, in particular the recurrent laryngeal nerve and parathyroid glands. Nonetheless, ideal patient selection criteria are not well established and society guidelines are lacking. The best candidates for this approach are small or average-sized (body mass index <30) young patients, with concerns of neck scarring, or have a history of keloid or hypertrophic scar formation. As mentioned above, this approach should only be offered to patients with a well-localized parathyroid adenoma preoperatively on imaging studies. Patients with higher possibility of MGD disease should not be offered this approach. This approach is usually deferred in patients with certain thyroid pathologies such as, locally advanced cancers, Graves' disease, Hashimoto's thyroiditis, or substernal goiter, and in patients with a previous history of surgery or irradiation of the neck. Patients should also be screened for contraindications that affect patient positioning during these procedures such as, rotator cuff pathology, shoulder/neck mobility problems, cervical spine disease, previous neck, chest, or axillary surgery.

Preoperative Considerations and Surgical Planning

Imaging before surgery can help guide the surgical approach by localizing the adenoma in many patients. Of all the imaging modalities US is the least expensive and least invasive, it does not involve radiation and is readily accessible. Parathyroid glands appear as well-circumscribed and oval, hypoechoic, and usually solid nodules. The sensitivity of US detection of parathyroid adenomas ranges from 27 to 95 %, with a specificity of 92–97 %. It is the operator experience that has the greatest effect and likely accounts for the wide range of reported sensitivity. The combination of US and Sestamibi scan may increase the accuracy of localization of a single adenoma to 94–99 %, as each modality contributes different data to help determine the gland location. Ultrasonography is more specific for anatomic location of the gland in relation to the thyroid, whereas scintigraphy is better at finding ectopic

glands especially in the mediastinum [28]. The availability of US has led some surgeons to further use it in the operating room. It can be used for identifying the parathyroid adenoma and its anatomical location just prior to surgery. US may also assist in precisely localizing the incision once the patient is in the neck extension position. Lastly, US guided FNA can be considered to confirm intrathyroidal parathyroid adenomas or in selected cases of persistent or recurrent hyperparathyroidism after failed exploration. An elevated PTH washout concentration from the FNA can help identify parathyroid gland lesions.

Four-Dimensional Computed Tomography (4D-CT) Scan generates exquisitely detailed, multilane images of the neck and allows the visualization of differences in the perfusion characteristics of hyperfunctioning parathyroid glands (i.e., rapid uptake and washout), compared with normal parathyroid glands and other structures in the neck. The images that are generated by 4D-CT provide both anatomic information and functional information in a single study that the operating surgeon can interpret easily and may serve an important role in localization before both initial and reoperative parathyroid procedures [29].

To further improve the surgical success of targeted parathyroidectomy and to minimize the possibility of persistent or recurrent hyperparathyroidism after surgery, some have advocated the use of surgical adjuncts such as IOPTH monitoring. Intraoperative PTH is useful in assessing the adequacy of resection by functional means without the need to expose all the parathyroid glands. The ability to confirm complete removal of all hypersecreting glands and predict operative success minimized operative time, diminished the need for bilateral neck exploration, and improved cure rates [30]. Intraoperative PTH is based on the short half-life of circulating PTH. Parathyroid hormone is cleared from the blood in an early rapid phase with a half-life variously reported as 1.5–21.5 min in patients with normal renal function. PTH levels are measured preoperatively and at set post-excision times. A decline of more than 50 % in PTH level from the highest pre-incision or pre-excision level is associated with predictive cure in 94–97 % of cases [31–33], especially when the levels drop into the normal range.

Surgical Technique

One of the advantages of the robotic-assisted approach is its facilitation of an endoscopic neck surgery while maintaining a three-instrument approach. It also gives the surgeon the ability to retract, view target surgical anatomy, and still have two arms to operate, while maintaining traction and counter traction. The robotic-wristed instruments permit the surgeon to reduce physiological tremors and increase the surgeon's operative free dexterity of movement. Three robotic instruments (Maryland dissector, ProGrasp forceps, and Harmonic curved shears) and a dual-channel camera are needed. By placing the camera through the axillary/retroauricular incision and using an endoscope with 30° down orientation, principles from the conventional cervical approach can be applied safely to this endoscopic technique. During development of the working space, electrocautery, a vascular DeBakey forceps, and various retractors (army–navy, right-angled and lighted breast retractors) are used for subcutaneous flap dissection and elevation (Table 26.1).

It is important for the surgeon to determine the best way to organize the operating room prior to the procedure. The operating table should be positioned where the anesthesiologist has access to the patient's airway. The patient cart is covered with sterile drapes and positioned on the contralateral side of the operating table. The patient cart is initially kept away from the operating table during the development of the working space to allow space for the surgical assistant to work across the table and retract the thyroid gland. Dr. Kandil routinely performs continuous nerve monitoring of the ulnar, radial, and median nerves to avoid neuropraxia when using the transaxillary approach. We also use intraoperative nerve stimulation to definitively identify motor nerve structures during the procedure.

Table 26.1 Equipment needed for the robotic-assisted transaxillary/retroauticular approach

Development of the working space • Electrocautery with a short, regular, and long tip • Vascular DeBakey • Army–navy retractors • Right-angled retractors • Breast lighted retractors[a]
Table devices • Chung's retractor, or Marina retractor (Marina Medical, Sunrise, FL, USA) • Laparoscopic suction irrigation • Laparoscopic clip appliers for hemostasis • Endo Peanut 5-mm device
Robotic instrumentation • 5-mm Maryland dissector • 8-mm ProGrasp forceps • 5-mm Harmonic curved shears • 30° endoscope (used in the rotated down position)
Robotic arrangement • Arm 1- Maryland dissector • Arm 2- Harmonic shears • Arm 3- ProGrasp forceps • Endoscope

[a]Transaxillary approach only

Robotic Transaxillary Parathyroidectomy

Step 1—Patients are placed in a supine position while under general anesthesia, and then intubated with a NIM transoral endotracheal tube (Medtronic Xomed, Jacksonville, FL, USA) to allow intraoperative monitoring of the recurrent laryngeal nerve function.

Step 2—Appropriate placement of the NIM endotracheal tube is confirmed by direct laryngoscopy and by visualization of the electromyographic waveform on the NIMS monitor.

Step 3—The neck is slightly extended, and the arm ipsilateral to the lesion is placed cephalad and flexed above the head (Fig. 26.1). This optimizes exposure of the axilla and creates a short distance from the axillary skin to the thyroid gland, through which dissection would be performed.

Step 4—Blood is drawn for a baseline rapid PTH serum level prior to prepping the neck or palpating the neck.

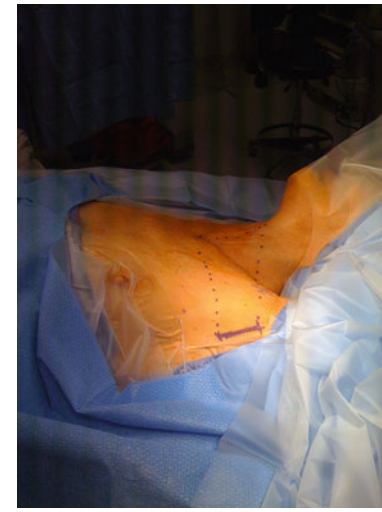

Fig. 26.1 Incision marking for robotic transaxillary parathyroidectomy

Step 5—The thyroid is identified by palpation and a vertical line is drawn from the midline of the thyroid to the sternal notch, demarcating the medical boundary of dissection. The inferior limit of dissection is drawn from the sternal notch to the ipsilateral axilla in a transverse manner. The superior limit of dissection is drawn in an oblique manner from the thyrohyoid membrane to the axilla (Fig. 26.1).

Step 6—Following infiltration with 10 mL of 1 % lidocaine with 1 in 200,000 adrenaline, a two-inch (5 cm) incision is then made with a scalpel from the intersection of the oblique line and the anterior axillary line as the superior limit and the intersection of the transverse line with the anterior axillary line as the inferior limit. Attention to detail in incising and handling the skin reduces cicatrix hypertrophy.

Step 7—Monopolar electrocautery under direct vision is then used to dissect to the pectoralis fascia. A subcutaneous flap is raised in the direction of the thyroid until the sternal and clavicular heads of the sternocleidomastoid muscle are visualized and opened.

Step 8—A retractor is used to elevate and retract the sternal head exposing the strap muscles. The natural dehiscence between the sternal and cla-

vicular heads is entered using the Harmonic Scalpel (Ethicon, Somerville, NJ, USA), allowing identification of the carotid sheath and ipsilateral omohyoid and sternohyoid muscles.

Step 9—The strap muscles are then elevated off the thyroid gland providing exposure from the sternal notch to the superior pole and across the midline.

Step 10—A wound protector is placed to protect the axillary wound edges from any heat generated by the electrocautery or the harmonic scalpel.

Step 11—A specially designed retractor (Marina Medical, Sunrise, FL, USA) is placed under the strap muscles and secured to the table mount lift to maintain an adequate working space without gas insufflation. This facilitates access to the posterolateral thyroid lobe.

Step 12—The da Vinci Si robot system is docked from the side of the bed contralateral to the operative field. The robotic instruments used are the ProGrasp forceps (Intuitive Surgical, Sunnyvale, CA, USA), Maryland Dissector (Intuitive Surgical, Sunnyvale, CA, USA) and Harmonic scalpel (Ethicon, Somerville, NJ, USA). The 30° endoscope is used in a downward facing orientation. The robotic arms are equipped with the Maryland dissector, the ProGrasp forceps, and the Harmonic scalpel. The Maryland dissector and Harmonic scalpel should be as far apart as possible. This is important in minimizing the risk of collision of the arms during the procedure.

Step 13—The thyroid gland is turned medially and with cautious dissection the pathological parathyroid gland is identified.

Step 14—The middle thyroid vein is divided using the Harmonic scalpel.

Step 15—Identification of the inferior thyroid pedicle with dissection RLN in tracheoesophageal groove is then undertaken to minimize the risk of injury to either structure.

Step 16—A nerve stimulator is routinely used by the assistant surgeon to confirm correct identification of the RLN.

Step 17—Once the pedicle has been delineated, the Harmonic scalpel is used to hemostatically seal and divide the small branches of the inferior thyroid artery close to the capsule of the adenoma.

Step 18—The parathyroid lesion is then dissected, excised, and delivered through the axillary incision (Video Clip 26.1).

Step 19—After gland removal, a serum sample is drawn for rapid PTH analysis. A 50 % or greater drop in PTH level and within normal range predicts a successful single gland surgery. The patient is kept sedated and surgical field maintained until the laboratory results are received. Those patients with no change in PTH level or inadequate reduction of the PTH likely have a secondary adenoma (or less likely an unappreciated MEN patient).

Step 20—The wound is irrigated and inspected for hemostasis. A Jackson-Pratt drain is coursed through the axilla and sutured to the skin.

Step 21—Meticulous closure of subcutaneous tissues and skin is performed using subdermal and subcuticular closure with fine attention to detail.

Robotic Retroauricular (Facelift) Parathyroidectomy

Step1—Patients are placed supine on the operating room table. The head is turned to the side contralateral to the side of the diseased gland. Patients are intubated using a NIM endotracheal tube size 6.0 (Medtronic Xomed, Jacksonville, FL, USA) to allow intraoperative monitoring of RLN function.

Step 2—A small portion of postauricular hair is shaved for the extension of the planned incision lines into the hair-bearing skin.

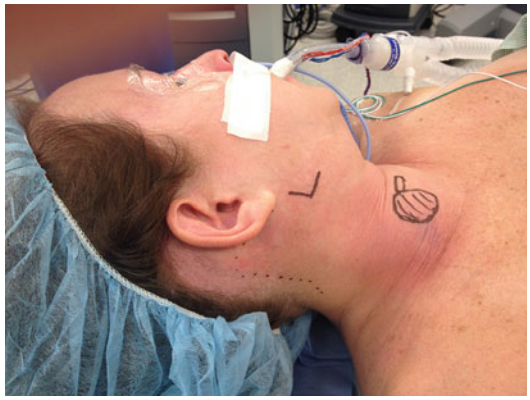

Fig. 26.2 Incision marking for robotic retroauricular parathyroidectomy

Step 3—The retroauricular incision is then marked out just posterior to the earlobe, extending into the postauricular crease and adjacent to the occipital hairline at a position that will be covered completely by the ear and hair at rest (Fig. 26.2).

Step 4—Blood is drawn for a baseline rapid PTH serum level prior to prepping the neck or palpating the neck.

Step 5—The flap is created superficial to the platysma using a Metzenbaum scissor. Care is taken to preserve the greater auricular nerve. Dissection in the plane superficial to the platysma is performed until the head of the sternocleidomastoid muscle is visualized.

Step 6—The space between the strap muscles and the SCM is created with electrocautery or Harmonic scalpel (Ethicon, Somerville, NJ, USA). The working space is created all the way to just above the omohyoid muscle, which correlates with the superior pole of the thyroid lobe.

Step 7—A specially designated retractor (Marina Medical, Sunrise, FL, USA) is then secured to the table mount lift and placed under the strap muscles to allow continuous exposure of the surgical field, maximizing access to the parathyroid gland.

Step 8—The da Vinci Si system (Intuitive Surgical, Inc., Sunnyvale, CA, USA) is then docked using the 30° scope, Maryland dissector, and a Harmonic scalpel (The camera is positioned in the center of the field, a Maryland grasper is placed in the nondominant hand, and the Harmonic is placed in the dominant hand). The robot is docked from the contralateral side of the operative field, with the 30° down looking endoscope, Harmonic scalpel, and Maryland forceps entering via the retroauricular incision.

Step 9—The thyroid gland is turned medially and with cautious dissection the pathological parathyroid gland is identified.

Step 10—The middle thyroid vein is divided using the Harmonic scalpel.

Step 11—Identification of the inferior thyroid pedicle with dissection RLN in tracheoesophageal groove is then undertaken to minimize the risk of injury to either structure.

Step 12—A nerve stimulator is routinely used by the assistant surgeon to confirm correct identification of the RLN.

Step 13—Once the pedicle has been delineated, the Harmonic scalpel is used to hemostatically seal and divide the small branches of the inferior thyroid artery close to the capsule of the adenoma.

Step 14—The parathyroid lesion is then dissected, excised, and delivered through the incision.

Step 15—After gland removal, a serum sample is drawn for rapid PTH analysis. A 50 % or greater drop in PTH level and within normal range predicts a successful single gland surgery. The patient is kept sedated and surgical field maintained until the laboratory results are received.

Step 16—The wound is irrigated and inspected for hemostasis.

Step 17—Meticulous closure of subcutaneous tissues and skin is then performed.

Robotic Thoracoscopic Mediastinal Parathyroidectomy

The presence of a thoracic surgeon is usually required for this procedure. This surgery is not done on an outpatient basis and requires a chest tube to be placed. This approach is utilized to avoid open thoracotomy or median sternotomy.

Step1—A left or right sided approach is chosen according to the location of the ectopic parathyroid gland. The patient is placed in a lateral decubitus position (depending on adenoma localization) with contralateral single-lung ventilation.

Step 2—A 10-mm port for the robotic endoscope is positioned in the 6th intercostal space in the anterior axillary line, and two 8-mm robotic operating ports are placed in the 4th intercostal space, a handbreadth right and left of the first incision.

Step 3—An accessory port is placed in the midclavicular line through the 6th intercostal space, through which a flexible retractor (US Surgical, Norwalk, Conn) is inserted to hold the lung away.

Step 3—A second accessory port through the posterior axillary line in the 6th intercostal space is provided for eventual suction.

Step 4—Resection of the parathyroid adenoma is performed by the thoracic surgeon at the console. This is done by incising either the parietal pleura covering the aortopulmonary window or pericardium depending on the location. The identification of the vagal and recurrent laryngeal nerves are encouraged, but are not considered to be an essential part of the procedure.

Step 5—The vascular pedicle is controlled with the harmonic scalpel or clips and once freed, the adenoma is removed. Compared to conventional thoracoscopic surgery, the robotic operating system provides better visualization of the operating field and facilitates the movement of the instruments. Radioguided surgery can be used but usually there is significant background activity from the heart.

Robotic parathyroidectomy is usually performed as an outpatient procedure. The patients are discharged on anti-inflammatory pain medication with narcotics only for breakthrough discomfort. Patients are supplemented with calcitriol 0.25 mcg twice daily and elemental calcium 1 g twice daily unless signs or symptoms of hypocalcemia present. No laboratory studies are required following intraoperative verification of serum PTH normalization. The patient's first outpatient follow-up is at 1 week for pathology review, wound inspection and further instruction on wound care. Duration and extent of vitamin D and calcium supplementation are based on preoperative bone mineral density determination and interdisciplinary management with an endocrinologist.

Summary

The results of the two prospective studies, two retrospective studies, and two case control studies are summarized in Table 26.2. All the reports of robotic parathyroidectomy have been shown to be safe, feasible, and efficacious. There are not studies in the literature that evaluate the outcome of robotic parathyroidectomy using the retroauricular approach. The preliminary results for robotic transaxillary and infraclavicular parathyroidectomy have shown it to be equivalent to conventional parathyroidectomy with regards to cure and complication rates. Complications such as recurrent laryngeal nerve palsy and hypoparathyroidism are rare (<1 %), similar to the conventional cervical approach. The preliminary functional outcomes of robotic parathyroidectomy are encouraging. Long-term prospective outcome data are imminent and randomized clinical studies are warranted to evaluate potential advantages. The conversion rate associated with robotic parathyroid surgery is unknown due to the sparse data in the literature. Nonetheless, conversion to a wider access or conventional procedure for bilateral neck exploration should not be considered a complication; it is a limitation of

Table 26.2 Best evidence studies in the English medical literature from January 2000–May 2015

Study (year)	Level of evidence	Sample size	Cohort	Mean operative time	Outcomes	Limitations
Prospective studies						
Landry et al. (2011) [9]	Level IIIA	2 pts	2 pts underwent RP for a PA Follow-up duration unknown	108.5 ± 9.2 min	Successful parathyroidectomy with no conversion; no intraoperative or postoperative complications; Biochemical cure achieved postoperatively	Small sample size; absence of control group; follow-up period unknown; No evaluation of patient reported outcome measures
Tolley et al. (2011) [7]	Level IIIA	11 pts	11 pts underwent RP for a PA Mean follow-up 6 months	Flap creation time, 31 min; console time, 51 min	Successful parathyroidectomy in all but 1patient who required a conversion to an open approach due to BMI of 33.4 kg/m^2; 1 patient was found to have persistent PHPT (due to nondiagnosed MEN1); no intraoperative or postoperative complications; excellent cosmetic outcome and patient scar satisfaction; significant improvement in quality of life	Small sample size; absence of control group; multiple remote ipsilateral incisions (1 infraclavicular and 3 incisions along the ipsilateral anterior axillary line, the inferior one translocated to a periareolar incision if body habitus permitted)
Retrospective studies						
Noureldine et al. (2014) [11]	Level IV	9 pts	6 pts underwent RP for a PA; 2 pts underwent RT for intrathyroidal PA; 1 pt underwent RP and RT for an atypical PA Mean follow-up 6 months	119 ± 15.6 min	Curative resection was established in all 9 cases 1 Patient required conversion to a transcervical approach due to the presence of multigland disease; no intraoperative or postoperative complications; Subjective cosmetic results excellent; Biochemical cure achieved in all cases	Retrospective study; small sample size; absence of control group; no evaluation of patient reported outcome measures

(continued)

Table 26.2 (continued)

Study (year)	Level of evidence	Sample size	Cohort	Mean operative time	Outcomes	Limitations
Karagkounis et al. (2014) [21]	Level IV	8 pts	8 pts underwent RP for PA Median follow-up 29 months	184 ± 58 min	Curative resection was established in all pts; No conversion was required; no intraoperative complications and only one postoperative complication, a case of postoperative seroma that was managed conservatively	Retrospective study; small sample size; no evaluation of cosmetic satisfaction
Case control studies						
Foley et al. (2012) [10]	Level IIA	16 pts	4 Patients underwent RP for PA; 12 patients underwent transcervical targeted parathyroidectomy (matched controls) Mean follow-up 6.1 months	186 ± 84.2 min (Control, 86 ± 27.9 min)	Curative resection was established in all patients; no intraoperative complications and only 2 postoperative complication, wound infection, and seroma (both treated conservatively); a learning curve was demonstrated	Small sample; no evaluation of patient reported outcome measures; short follow-up for one patient (2 weeks)
Tolley et al. (2014) [22]	Level IIA	30 pts	15 pts underwent RP for PA; 15 patients underwent transcervical, focused lateral parathyroidectomy (matched controls) Minimum follow-up 12 months	119 min (control, 34 min)	Curative resection was established n 97 % of pts; conversion required in one case due to large body habitus (33.4 kg/m^2); a learning curve was demonstrated; excellent cosmetic outcome and patient scar satisfaction; significant improvement in quality of life	Although largest study, small sample size; multiple remote ipsilateral incisions (1 infraclavicular and 3 incisions along the ipsilateral anterior axillary line, the inferior one translocated to a periareolar incision if body habitus permitted)

PA parathyroid adenoma, *RP* robotic parathyroidectomy, *min* minutes, *pts* patients, *MEN1* multiple endocrine neoplasia type 1

the preoperative localization studies and focused surgical approach rather than a reflection of the robotic technique per se. Nevertheless, a high conversion rate may reflect poor patient selection. Additionally, prolonged paresthesia of the skin flap, and muscle stiffness has been described by some patients undergoing the transaxillary approach. The arm positioning can cause overtraction and brachial plexus neuropraxia. Using the intra-op somatosensory evoked potential responses (SSEP) nerve monitoring should help avoid these complications. After facelift parathyroidectomy, transient hypesthesia in the distribution of the greater auricular nerve is universal.

Another significant disadvantage of robotic surgery is the cost of the procedure. Studies of the transaxillary approach suggest that increased operative time, coupled with the capital expense of the robotic system and the specialized equipment required may significantly increase the cost of surgery. While compensation for robotic procedures is significantly higher than conventional approaches in Asia, there is not increased reimbursement in the USA.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion

Robotic parathyroidectomy approaches offer the distinct advantage over anterior cervical approaches of completely eliminating a visible neck scar. Precise preoperative imaging enables the careful planning of robot-assisted surgery for ectopic parathyroids located at relatively inaccessible regions such as the anterior mediastinum. Despite the advantages of the robotic technology and excellent results in terms of complication and cure rates, there are some concerns for its routine application in clinical practice. Experience of the entire surgical team with robotic technology is essential for optimizing outcomes using this procedure. Inserting and aligning the instruments requires a trained assistant and a team approach. We believe consistency of the team members including operating room staff yields the utmost improvements over time. In addition to mastering the technical aspects of the robotic surgical system, surgeons need to become familiar with the anatomic perspective of the lateral approach to the thyroid and parathyroid glands.

The adoption of new technology in the operating room offers potential benefits as well as economic challenges. The need for specific instrumentation has been considered a source of additional costs compared with conventional surgery. Operative time, which was considered one of the limits of the technique, has been demonstrated to decrease with increasing experience.

Robotic surgery in the head and neck is still in the developmental stages. There is no question that it has restored the two-handed wristed manipulation and depth-of-field visualization to surgical procedures that had lost these capabilities during a transition to endoscopic surgery. What remains to be performed is a balanced investigation with rigorous data analysis to fully explore and recognize its advantages and limitations. At present, robotic parathyroidectomy can only be justified in patients who are predisposed to keloid or hypertrophic scarring or have cultural considerations leading to the desire to avoid a neck scar.

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Part VII

Special Topics

A History of Hyperparathyroidism

27

Orlo H. Clarkv

Contents

Introduction

Endocrine disorders are primarily caused by increased or decreased secretion of a hormone (from the Greek word first proposed in 1905 by Starling, meaning to excite, arouse, or set in motion) [1]. The first mentioned endocrine operation in antiquity was castration [2]. The last endocrine gland to be discovered was the parathyroid gland [3]. These tiny millet-sized structures are situated near the thyroid gland in the neck and were often inadvertently removed during thyroid operations that caused hypocalcemia and tetany. Parathyroid glands could also become neoplasms and secrete too much parathyroid hormone thus resulting in hypercalcemia with kidney and/or bone disorders. In this chapter I will clarify the progress leading to the discovery of primary hyperparathyroidism and how it should most effectively be treated.

In the eighteenth century John Hunter (1728–1793), the English anatomist and surgical scientist, noted that "only one testicle was necessary to maintain normal sexual function and that castration prevented the growth of antlers in a stag" [4]. He also reported the effects of the transplantation of a cock's testis to the abdomen of a hen and the subsequent change of secondary sex characteristics as well as the importance "of the testes for maintaining the seminal vesicles, prostate and Cooper's gland" [5]. Arnold A. Berthold

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(1803–1861), however, was the first to suggest that the testes maintained secondary sex characteristics by acting directly in the blood.

At about the same time as Hunter, the Swiss scientist Albrecht von Heller (1708–1777) from Berne, Switzerland identified the thyroid, thymus, and spleen as organs without ducts that secreted substances directly into the blood [6]. The concept of internal secretion with organs secreting substances directly into the blood stream was not generally accepted until the French physiologist Claude Bernard (1833–1878) reported that the liver secretes sugar directly into the portal vein (internal secretion) and bile into the common bile duct (external secretion). Bernard suggested that the spleen, adrenals, thyroid, and lymph glands functioned by internal secretion [6]. In 1855 Thomas Addison (1793–1860), a physician at Guy's Hospital in London, reported that absence or destruction of the supra renal or adrenal glands in man causes disease and death [7]. Following Addison's report, Charles J.E. Brown-Sequard (1817–1894) removed adrenal glands from rats. Although his results were not entirely convincing because of inconclusive findings, and death from the operation itself, he observed that the animals had symptoms similar to those occurring in patients dying from Addison's disease. He suggested that the adrenal glands are essential for life [8].

By the end of the nineteenth century thyroidectomy was an accepted operation. Unfortunately some patients developed postoperative myxedema, caused by thyroid hormone deficiency, and some tetany, because of inadvertent parathyroidectomy causing parathyroid hormone deficiency and hypocalcemia. In 1891 George Murray, a pathologist and physician from Newcastle-upon-Tyne, successfully treated a woman with an endocrine deficiency, myxedema. When he injected sheep thyroid tissue into this patient with severe hypothyroidism, she experienced a dramatic clinical improvement [9]. One year later Edward Fox of Plymouth, England reported that "half a sheep's thyroid, lightly fried and taken with currant jelly once a week was also effective." in treating myxedema [10]. This was the first successful demonstration of organotherapy, the treatment of an endocrine deficiency with preparations derived from endocrine glands.

Anatomy and Microscopy of the Parathyroid Glands

Sir Richard Owen (1804–1892) the Conservator of the Hunterian Museum, Royal College of Surgeons, London and Natural History Department, British Museum, identified a parathyroid gland in the Indian one horned rhinoceros from the London zoo. This Rhino died from a fractured rib and injured lung after an attack by an elephant [11]. Owen presented his autopsy findings of "a small, compact yellow structure in the expected location in the neck of the rhinoceros" at the Zoological Society on February 12, 1852. He preserved the trachea. This structure can be seen today at the Hunterian Museum of the Royal College of Surgeons. The related article was not published, however, until 1862. Owen's successor A.J.C. Cave, the Professor of Anatomy at the Royal College of Surgery, discovered that Owen's article was originally published in 1852, not 1862, thus making Owen the first person to identify a parathyroid gland in animals [12].

In 1852, the same year as Owen's original presentation on the parathyroid gland Ivar Viktor Sandstrom (1852–1889) was born in Sweden. While working as a medical student in the Anatomy Department at the University of Uppsala in 1877 as a research assistant for Professor Edward Clasen, he identified parathyroid glands first in dogs and subsequently in the cat, rabbit, ox, horse, and man [13, 14]. He was surprised that other anatomists had not observed these glands. His extensive studies included dissections of 50 human cadavers. He suggested the name of "glandulae parathyroideae" [15]. First publishing on this subject in 1880, he writes "Almost 3 years ago I found on the thyroid of a little dog a tiny growth, barely the size of a hemp seed which lay enclosed within the same capsule of tissues as that gland, though it was dissimilar in its lighter color" [16–18]. When Sandstrom submitted his 31 page article on the discovery of

the parathyroid gland to the prestigious German press, it was rejected [17]. He was invited, however, to present his findings at the meeting of the Scandinavian Society of Natural Science in Stockholm in 1880. Even though there was little interest in his discoveries, the same year he received the Hwasser Award from the Uppsala Medical Association for his work in this field [18]. During his presentation Sandstrom described the size, shape, color, blood supply, and histology of the normal parathyroid glands which he noted were not lymph nodes. "He postulated that the glands were an embryonic extension of the thyroid arrested in various stages of development and he astutely recognized that their location varied in animals and man" [13]. He also acknowledged that in 1855 Robert Remak (1815–1865), an embryologist at the University of Berlin, had described "a parathyroid gland as being associated with the thymus and distinct from the thyroid" [19]. In 1863 Rudolf Virchow (1821–1902), the famous pathologist from the University of Berlin, also identified a parathyroid gland that he believed was a distinct structure and was not ectopic thyroid tissue or a lymph node. There was no follow up by Remak or Virchow, but subsequent anatomical and histological studies by A Kohn in 1895 confirmed Sandstrom's findings that the parathyroid glands were not thyroid tissue [20]. Sandstrom suffered from severe depression and committed suicide on June 2, 1889. He is credited with "the last discovery of an organ in humans, an honor he surely would have cherished" [20].

Parathyroid Gland Function

Eugene Gley (1857–1930), Professor of Physiology and the Brown-Sequard Chair at the College de France in Paris studied the parathyroid glands because of his interest in the function of the thyroid gland. Gley was aware of Sandstrom's discovery of the parathyroid glands from his reading in the atlas of rabbit anatomy "Die Anatomie des Kaninchens" by W. Kraus published in 1884 [21]. The text made reference to Sandstrom's previous publication. Gley's experiments in dogs documented that removal of four parathyroid glands usually resulted in tetany (a term from the Greek word tetanus "to stretch" first used in 1852 by Lucien Covisart, the personal physician of Napoleon III). The term was popularized by the French clinician Armand Trousseau (1801–1867) in his lectures [20, 22]. Gley's findings, as published in 15 articles from1881 to 1897, proved that removal of the parathyroid glands and not the thyroid gland was responsible for postoperative tetany. Soon after Gley's findings, Julio Vassale (1862–1912) and Francesco Generali (1896) and others also reported that parathyroidectomy, and not thyroidectomy, resulted in tetany [23].

Of interest was that parathyroidectomy is more harmful regarding blood calcium levels than simultaneous excision of both the thyroid and parathyroid glands [24]. It wasn't until 1962 that Douglas Copp and colleagues in Vancouver documented that a calcium lowering hormone (calcitonin) is present in the thyroid gland [25]. In 1901 Jacob Loeb (1859–1924), a professor of biology at the University of California, Berkeley, reported that he could effectively treat neuromuscular irritability caused by hypocalcemia, by giving calcium [22]. James B. Collip and Clark developed a method for measuring the concentration of calcium in the blood that became the standard method for determining blood calcium for many years in most laboratories [24].

Vassale and Generali and many others including Gley believed that the parathyroid glands have an antitoxic function. Support for this theory was provided by Arthur Biedl in 1907, who reported that blood-letting and transfusion of normal blood relieved the symptoms of tetany in parathyroidectomized animals [26]. In 1909, MacCallum (1874–1944) and Voegtlin (1879–1960) at Johns Hopkins in Baltimore and others confirmed the results of these experiments, and reported that blood-letting either relieved the tetany or made it less severe. They subsequently stated that post-parathyroidectomy tetany was associated with hypocalcemia [27]. In 1924 Noel Paton reported "that complete removal of the parathyroid tissue leads to a fatal toxemia; he further suggests that the parathyroids through their

internal secretion control the tone of muscles by regulating metabolism, i.e., the production and destruction of guanidine in the body" [28].

In 1924 A Hanson (1888–1959) from Minnesota first prepared and patented an effective parathyroid extract [29]. One year later J. Collip (1892–1965) from Edmonton, Alberta prepared a purer parathyroid extract [30]. Collip addressed the question regarding the cause of post-parathyroidectomy tetany. He stated "that a very strong case has been made out for the guanidine intoxication theory of post-parathyroidectomy tetany. The evidence, however, consists so largely of the circumstantial type that it fails to carry with it the weight of final conviction" [25]. In 1924 Collip documented that the injection of his parathyroid extract effectively treated post-parathyroidectomy tetany, thus disproving the toxin theory.

In 1923 the Norwegian physician—scientist Harold Salveson also addressed the etiology of post-parathyroidectomy tetany. He documented "that complete parathyroid ablation invariably lowered the blood calcium, that the blood sugar level was not altered and that guanidine accumulation occurred only terminally during agonal convulsions" [31]. These observations as well as the presentation of tetany after parathyroidectomy in humans documented both the etiology of the tetany and the importance of preserving the parathyroid glands during thyroid operations.

Parathyroid autotransplantation was done in the early nineteenth century and helped confirm the function of the parathyroid glands. In 1909 William Halsted reported that parathyroid transplantation was "successful in 61% of the cases in which a deficiency greater than one half has been created" [32]. Excision of the auto transplanted parathyroid gland in animals that had previously had all parathyroid glands removed resulted in tetany.

Hyperfunction of the Parathyroid Glands and Bone Disease

In 1891 during a festschrift lecture for Rudolf Virchow (1821–1902) Friedrich von Recklinghausen (1833–1910), a professor of pathology from Strasbourg, presented three patients with osteitis fibrosa cystica and bone tumors. One of these patients had a "reddish brown lymph node" below the thyroid [22]. The lymph node was probably a parathyroid tumor. In 1904 Max Askanazy (1865–1940), a pathologist from Tubingen, documented that multiple abnormal parathyroid glands were present in patients with osteomalacia as well as in rats with rickets [33]. He also identified a probable parathyroid tumor in a patient with osteitis deformans but did not confirm it histologically until 1930 [22]. C.E. Benjamins and J.P.L. Hulst each identified a probable parathyroid tumor by gross and histological examination as did other surgeons prior to 1910 [34].

In 1906 Jacob Erdheim (1874–1937) from Vienna made the important observation that when he cauterized and destroyed the parathyroid glands in rats, they not only developed tetany, as reported by Gley, but also developed abnormal calcification of the teeth. He thought that both conditions were the result of hypoparathyroidism [22]. These observations encouraged him to examine the parathyroid glands in patients who died with bone disease. In 1907 he reported the presence of hyperplasia of the parathyroid glands in patients with osteomalacia, and in 1911 he observed parathyroid hyperplasia in rachitic rats [22]. At this time most experts who were interested in bone disorders thought that the parathyroid glands became enlarged to compensate for the bone disease. The finding of one abnormal parathyroid gland with other normal parathyroid glands rather than all parathyroid glands being abnormal conflicted with this hypothesis. In 1915 Freidrich Schlagenhaufer (1866–1930) from Vienna suggested that a parathyroid tumor is responsible for the bone disease rather than the reverse [35]. He described two patients with severe bone disorders who had solitary parathyroid tumors and recommended parathyroidectomy [36]. In 1925 his observations were supported by the studies of Hoffheinz, who reported that 85% of 44 patients with von Recklinghausen's bone disease had only one abnormal parathyroid gland. He concluded that primary hyperparathyroidism is more likely to be the cause of the bone disease rather than a consequence of the bone disease [37].

Parathyroid Surgery and Remarkable Patients

In 1910 Albert J. Ochsner and Ralph L. Thompson, in their textbook titled *Thyroid and Parathyroid Glands* reported that a number of solitary parathyroid tumors was observed by surgeons and pathologists [38]. "Most of these growths have been of small size" [39]. Weichselbaum from Stuttgart and others suggested that these be called adenomas "although a distinct boundary line between adenoma and hyperplasia cannot be sharply drawn" [40]. Erdheim, MacCallum, Weichselbaum, Verebely, Goris, and others found parathyroid tumors in patients with osteitis fibrosa cystica, and most were solitary tumors [40].

The first patient with primary hyperparathyroidism and osteitis fibrosa cystica (von Recklinghausen's syndrome) to be successfully treated by parathyroidectomy was operated on by Felix Mandl (1892–1957) at the second surgical unit in Vienna, Austria. The patient Albert Jayne was a 34-year-old street car conductor who had a 5-year history of fatigue, bone pain, and progressive weakness, especially in his legs [41]. X rays of his bones documented osteopenia and bone cysts in his pelvis and both femurs. Because of Erdheim's studies suggesting that the bone disease was the primary cause of his clinical problems, Mandl first treated Albert with Collip's parathyroid extract. Unfortunately it did not help. Jayne's situation worsened as he fractured his leg and developed white urine, which can be caused by extreme hypercalciuria. Following the same reasoning, Mandl therefore transplanted four freshly acquired normal parathyroid glands into Albert's abdomen, but this remedy also proved to be ineffective. Therefore, on July 30, 1925 Mandl explored Albert's neck and removed a 2.5×1.5×1.2 cm left lower parathyroid tumor that was adherent to his recurrent laryngeal nerve. Mandl also identified three other normal parathyroid glands. Postoperatively, Jayne's condition improved and his blood and urinary calcium levels returned to normal. It is surprising, however, that he did not develop tetany immediately postparathyroidectomy since he certainly should have had bone hunger.

Approximately 4 months after Jayne's parathyroid operation, his bone density improved and having formerly been bedridden, he was now able to walk with crutches [42]. Unfortunately, he subsequently developed recurrent hyperparathyroidism which is uncommon except in patients with familial hyperparathyroidism, secondary hyperparathyroidism due to renal failure or parathyroid cancer. In 1927 one of Mandl's colleagues in Vienna, E. Gold, operated on another patient with osteitis fibrosa cystica and successfully removed a parathyroid tumor. Gold first suggested the name hyperparathyroidism [43].

The Merchant Sea Captain Charles Martel was the first reported patient diagnosed with primary hyperparathyroidism in the United States and he had the first parathyroid exploration in 1926. He was initially diagnosed with hyperparathyroidism by Dr. Eugene Dubois (1882–1959) at Cornell Medical School and Bellevue Medical Center in New York City. Dubois discovered that Martel had hypercalcemia and ostitis fibrosa cystica. Although unknown to Dubois and subsequently Aub, Martel had clinical manifestations similar to Jayne's in Vienna, including bone fractures and kidney stones [44].

Dr. Dubois referred Martel to his colleague Joseph C. Aub (1890–1973) at Massachusetts General Hospital where Aub was studying lead poisoning because his own metabolic unit was closed for the summer [41]. These investigators were aware that calcium and lead were stored in bone in a similar fashion. Aub and his colleagues questioned whether injection of parathyroid extract might help patients with lead poisoning by helping to mobilize lead from the bone. After a thorough metabolic evaluation at the MGH and confirmation of the presence of hypercalcemia, Martel was referred for parathyroidectomy. This operation was performed May 1926 by Elliot P. Richardson, Chief of Surgery at the MGH in Boston. During this procedure Dr. Richardson removed a normal right lower parathyroid gland. Four other nodules were also removed. Unfortunately, the sea captain remained hypercalcemic and symptomatic so that a repeat neck exploration was performed with the removal of a second normal parathyroid gland from his left

neck as well as five other nodules, again without success.

Three years later in 1929 at Cornell Medical Center Martel had his third negative neck exploration, this time performed by Dr. Russell Patterson. Again, no abnormal parathyroid glands were observed or removed. When Martel's symptoms persisted, however, he was readmitted to the MGH in May of 1932. Since the time of Martel's initial treatment at the MGH, Fuller Albright (1900–1969), a talented physician who had spent a year doing research with Jacob Erdheim in Vienna worked with Aub and his associate Walter Bauer (1898–1963). By this time Albright had become the director of the metabolic clinic, and calcium was one of his primary interests. Edward Churchill had also replaced Elliot Richardson as chief of surgery in 1931. Churchill as well as Bauer and Albright encouraged Oliver Cope, a talented surgical intern, to work with Benjamin Castleman, an equally talented pathology resident, to study the parathyroid glands during autopsy. By this time Albright and his medical colleagues had diagnosed four other patients with presumed primary hyperparathyroidism. All four were awaiting parathyroidectomy. The physicians, however, were reluctant to have patients with primary hyperparathyroidism operated on by surgeons with little or no experience in this field [45].

In 1932 Cope and Churchill performed their first successful parathyroidectomy at the MGH. After this procedure, however, Churchill apparently told Cope that he was "too rough, and the field was too bloody" [45]. Despite their increasing surgical experience in treating patients with primary hyperparathyroidism Cope and Churchill re-operated on Captain Martel three more times without success. Luckily, the Swedish pathologist Hilding Bergstrom reported that at autopsy a patient was found to have a parathyroid tumor in his mediastinum that had previously been observed on X ray [46]. This finding was listed in the Index *Medicus* and came to the attention of Albright and his colleagues. Although reluctant to perform a seventh operation, Oliver Cope and Edward Churchill did re-operate on Martel and subtotally resected a mediastinal parathyroid tumor via a median sternotomy. Despite success and resolution of some symptoms Martel developed renal failure and urinary sepsis and died several weeks following surgery.

The first successful parathyroidectomy in the United States for a patient with primary hyperathyroidism was performed in August, 1928 by Dr. Isaac Olch in St. Louis, Missouri. This patient presented with nephrolithiasis, osteitis fibrosa cystica, and hypercalcemia. Following removal of a parathyroid adenoma, she developed tetany but subsequently had relief of her pre and postoperative symptoms and a normal blood calcium level [22].

In 1932 Albright noted that about eighty percent of patients diagnosed with hyperparathyroidism and osteitis fibrosa cystica also had kidney stones. He therefore screened patients with kidney stones and quickly identified a patient with renal stones without bone disease. The patient was subsequently proven to have a parathyroid tumor. Albright and his colleagues also identified patients with primary hyperparathyroidism without either kidney stones or osteitis fibrosa cystica. Nephrolithiasis and nephrocalcinosis became the most common key to the underlying diagnosis of primary hyperparathyroidism and reasons for parathyroidectomy. Other associated medical problems that occurred more often in patients with primary hyperparathyroidism include peptic ulcer disease, and pancreatitis [47]. By July 1960 routine serum multianalysis (SMA) 12, screening of blood levels for calcium was first introduced at Barnes Medical Center in St Louis [48]. Primary hyperparathyroidism with minimal symptoms or complications became the most common form of this disorder and a common rather than a rare endocrine problem.

Surgical Treatment of Primary Hyperparathyroidism

Most surgeons interested in parathyroid surgery based on the results at the MGH and other leading medical centers have recommended bilateral neck exploration with identification of four para-

thyroid glands and removal of the abnormal parathyroid gland or glands [49]. In 1966 Oliver Cope and colleagues reported that 77 % of the 343 patients with confirmed primary hyperparathyroidism at the MGH had a solitary parathyroid tumor, 17 % had hyperplasia and 4 % double adenomas [45]. In 1966 Leon Goldman and colleagues at the University of California, San Francisco reported that 92 % of their 300 patients with primary hyperparathyroidism had a solitary adenoma, 4 % a double adenoma, 3 % hyperplasia and 1 % parathyroid carcinoma [49]. Dr. C.A. Wang, who became the parathyroid surgeon at the MGH after Dr. Cope, as well as Sten Tiblin and Anders Berganfelz from Sweden, and Colin Russel from Northern Ireland recommended a unilateral operation, when possible, rather than a bilateral exploration. [50–52, 67, 68] In contrast, Edward Paloyan and A M. Lawrence and W. F. Ballinger and R. C. Haff recommended a subtotal parathyroidectomy for all patients with primary hyperparathyroidism regardless of the operative findings [53, 54]. The latter experienced surgeons stated that it was difficult for surgeons and pathologists to distinguish grossly or histologically between a hyperplastic and adenomatous parathyroid gland and that parathyroid hyperplasia was becoming more common. Orlo Clark and Leon Goldman, however, disagreed with these recommendations and stated that one must differentiate between persistent hyperparathyroidism caused by leaving abnormal parathyroid tissue and recurrent hyperparathyroidism caused by new growth of one or more of the remaining parathyroid glands. The former is relatively common and influenced mostly by the lack of surgeon's experience. The latter is uncommon except in patients with familial hyperparathyroidism, parathyroid cancer, or parathyromatosis [55]. Most of the "recurrences" in Paloyan's patients and Ballinger and Haffs' patients were the result of persistent disease caused by failure to remove enough abnormal parathyroid tissue and not by new growth. Some of their patients also had true recurrent hyperparathyroidism, but most of these patients had familial disease [55]. Clark and Goldman suggested that subtotal thyroidectomy would increase the risk of hypoparathyroidism and should not be done.

In the 1970s ultrasound and thallium scanning became available, and with increasing experience the abnormal parathyroid gland could be localized in about 50–80 % of patients. When sestamibi scanning became available in the 1980s, it became the most popular parathyroid localizing test [56]. Localization tests were not thought to be necessary when a bilateral neck exploration was planned, but a positive scan can help direct the surgeon to the most abnormal parathyroid gland and also identify parathyroid tumors in ectopic positions. Localization studies are most accurate in patients with solitary rather than multiple abnormal parathyroid tumors.

Since the 1990s and the advent of more accurate localization tests and the availability of intraoperative parathyroid hormone testing with rapid PTH assay as recommended by Dr Irvin, many parathyroid surgeons recommend a minimally invasive, scan directed approach [57, 58]. Numerous expert surgeons have reported similar success rates (about 97 %) when compared to the traditional bilateral approach [59, 60]. Some experienced surgeons still recommend a bilateral approach, which has been the gold standard [61]. Other recently reported approaches for parathyroid removal include videoscopic and remote access surgery [62, 63]. Minimally invasive surgery using a small, approximately 2 cm incision with endoscopic instruments, magnification and lighting is also a popular approach.

Summary

Primary hyperparathyroidism was initially diagnosed in patients with crippling bone disease and subsequently with the presence of kidney stones and nephrocalcinosis. Today in the USA and Europe, most patients with primary hyperparathyroidism are detected by routine determination of blood calcium levels. Although about 20 % of patients with primary hyperparathyroidism still present with kidney stones, most have only mild symptoms. Many surgeons recommend parathyroidectomy for all patients with hyperparathy-

roidism who have no contraindications to surgery. Some endocrinologists and other specialists use specific criteria for selection for parathyroidectomy [64–67].

Best Practices: N/A

Society Guidelines: N/A

Expert Opinion: N/A

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No EBM classifications were made of historical references.

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Primary Hyperparathyroidism; Current Management Guidelines

28

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Introduction

The diagnosis of primary hyperparathyroidism (PHPT) is made when the total serum or ionized calcium is elevated and the concentration of parathyroid hormone is concurrently elevated, or inappropriately within the normal reference range. The most likely surgical finding in PHPT is a single, benign adenoma (about 80 %) with the remaining patients demonstrating multiglandular, hyperplastic disease, rarely multiple adenomas, and even more rarely parathyroid carcinoma [1]. Prior to the advent of the multichannel autoanalyzer in the 1970s, PHPT often presented with overt, symptomatic disease characterized primarily by kidney stones, radiological skeletal involvement, symptomatic hypercalcemia, generalized weakness, and neurocognitive complaints [2]. The change in the clinical presentation of PHPT, from primarily a symptomatic to an asymptomatic disorder, can be traced to widespread screening of the population when serum calcium became routinely measured. With this milder, asymptomatic presentation of PHPT in most developed countries, more sophisticated investigative methods became necessary to determine whether target organs were involved. The central question that has been repeatedly addressed over the past 25 years is who among patients with asymptomatic PHPT should be referred for parathyroidectomy

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and who can be safely followed without surgery? This question has been the subject of 4 International Workshops on the Management of Asymptomatic PHPT [3–9]. In this chapter, we summarize the evidence and recommendations of the most recent Workshop that was held in Florence, Italy in 2013.

Renal Disease

Under physiological conditions, serum calcium is confined to a very narrow, normal range, through a precise interplay between the parathyroid glands, bone, kidneys, and the gastrointestinal tract. Ordinarily, PTH secretion by the parathyroid glands is suppressed by rising extracellular ionized calcium. However, in PHPT, the aberrant gland(s) becomes less sensitive to negative feedback and PTH secretion continues inappropriately [2]. The abnormal PTH secretion leads to increased bone turnover, which in turn leads to greater calcium efflux into the extracellular space, increased filtered calcium, and increased renal tubular calcium reabsorption [10]. The increased filtered calcium is believed to contribute to the development of nephrocalcinosis and nephrolithiasis; still the most common complications of PHPT.

In a retrospective analysis of 141 patients with PHPT without previous renal involvement, the incidence of asymptomatic kidney stones detected by routine abdominal ultrasound was 11.4 % compared to 2.1 % in control subjects [11]. This incidence was higher in a prospective study of 140 consecutive patients with PHPT where routine ultrasound detected asymptomatic kidney stones in 55 % of subjects [12]. Other than hypercalcemia and hypercalciuria, neither study examined additional risk factors for stone formation that may have accounted for the observed difference in stone frequency [12]. Nonetheless, both studies demonstrated that asymptomatic kidney stones are more common in patients with PHPT than the general population [11, 13], lending support to the recent guideline revision that advocates systematic screening for kidney stones and kidney stone risk factors.

Skeletal Involvement

Bone is a dynamic tissue undergoing constant remodeling [14]. In PHPT, bone remodeling is increased as a result of excess PTH [15]. By dual energy X-ray absorptiometry (DXA) and analysis of iliac crest bone biopsies, a clear bone phenotype, with preferential loss of cortical bone, has been demonstrated in mild asymptomatic PHPT [16–19]. While these well-established findings are consistent with the notion that PTH has a proclivity to resorb cortical bone, they are not consistent with data reporting on fracture incidence in this disorder. For example, a retrospective cohort analysis of 407 patients with PHPT demonstrated a significantly increased incidence of fragility fractures at skeletal sites regardless of whether they were enriched in trabecular or cortical bone [20]. This included a greater than threefold incidence of vertebral fractures and a greater than twofold incidence of Colles', rib, and pelvic fractures. Furthermore, systematic radiographic evaluation of 150 consecutive postmenopausal women with PHPT revealed a 25 % vertebral fracture incidence compared to 4 % incidence in matched controls [21].

In addition to clinical findings, newer imaging technologies have helped clarity the extent to which trabecular bone is a target of PTH action in PHPT. High-resolution peripheral quantitative computer tomography (HRpQCT) has facilitated noninvasive in vivo assessment of bone microstructure ([22]; Fig. 28.1). Studies utilizing HRpQCT to assess bone microarchitecture at the distal radius and tibia in women with untreated PHPT compared to healthy age-matched controls demonstrated that the skeletal abnormalities in PHPT are present in both the cortical and trabecular compartments [23, 24]; (Fig. 28.2). Hansen and colleagues noted reduced cortical area, total cortical volume (area minus cortical porosity), and cortical thickness at the radius. Furthermore, at the radius, trabecular number was reduced, resulting in increased trabecular separation and reduced trabecular volume. At the tibia, no significant differences in cortical or trabecular parameters were noted. Although sample size could have limited significant findings at the tibia, the tibia is also a weight bearing bone. Thus,

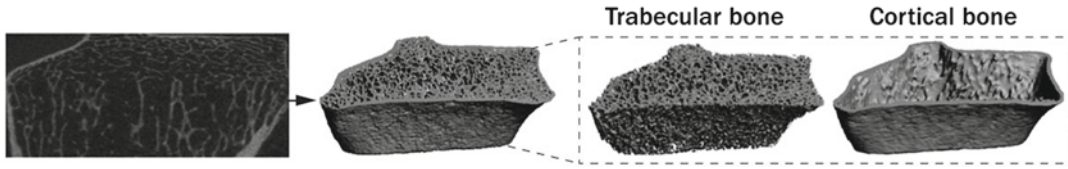

Fig. 28.1 HRpQCT image of the distal radius; separated according to cortical vs. trabecular components [48]

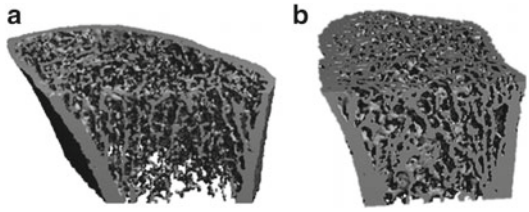

Fig. 28.2 Representative HRpQCT images of the distal radius of PHPT (**a**) and control (**b**) subjects [49]

differential mechanical loading (tibia greater than radius) could account for these differences [23]. Stein et al. found reduced cortical volume at *both* the distal radius and tibia. With regard to trabecular microstructure at the radius, trabecular number and thickness were reduced resulting in increased trabecular separation and reduced trabecular volume. At the tibia, only trabecular volume and separation were negatively impacted [24].

HRpQCT findings, which document that the trabecular compartment is involved in the skeletal disease of PHPT, have been further substantiated by trabecular bone score (TBS). TBS estimates trabecular microstructure through analysis of pixel gray-level variations derived directly from the DXA image of the lumbar spine. A lower TBS value reflects a more porous, heterogeneous trabecular network and reduced bone strength. TBS values for microarchitecture are described in tertiles: normal, partially degraded, and degraded [25]. TBS was degraded or partially degraded in the majority of PHPT patients in one cohort despite the majority of subjects demonstrating normal spine bone mineral density (BMD) by DXA [26]. Similarly, in a case-control study, despite no difference in spine BMD by DXA, TBS was lower among patients with PHPT [27]. Furthermore, in this patient population, TBS was significantly correlated with many trabecular and cortical HRpQCT parameters at both the distal radius and tibia [26].

As a result of this more recent appreciation that in PHPT, skeletal involvement is likely more generalized and not restricted to the cortical compartment, the revised guidelines suggest a more proactive approach with systematic screening for complications within the trabecular compartment, namely vertebral compression fracture detection, in addition to DXA testing.

Natural History Without Surgery

The longest observational study of patients with asymptomatic PHPT was conducted over 15 years, detailing the natural history of 49 patients who did not meet surgical criteria or refused parathyroidectomy [19]. PTH, renal function, and urinary calcium excretion remained stable for 13 years, but serum calcium subsequently started to rise slightly. Despite the slight increase in the average serum calcium concentration at these later time points, no patient developed kidney stones during the follow up period. During the first 8 years of observation, BMD by DXA did not change at any site in this cohort. Thereafter, while lumbar spine BMD remained stable, both femoral neck and distal 1/3 radius sites declined by 10 % or more in the majority of patients. Overall, of these 49 subjects, 18 patients (37 %) progressed to develop new surgical criteria during the study period.

Guidelines on the Management of Asymptomatic PHPT

There is no controversy over the recommendation that symptomatic patients should all be considered for parathyroid surgery if there are no medical contraindications. The point of guidelines is to provide assistance on the management of patients

with asymptomatic PHPT. Since 1991, these guidelines have been revised three times, most recently in 2013, to take into account the latest advances in knowledge about this predominant form of the disease [3, 6, 8, 9].

Initial Evaluation of Asymptomatic PHPT

The initial approach to patients with asymptomatic PHPT should focus on identifying patients at risk for fragility fractures and kidney stones (Table 28.1). These points have been noted above but are presented here along with other aspects of the evaluation that may lead to the recommendation for surgery. Consistent with previous guideline recommendations, all patients should have BMD measured by DXA at the lumbar spine, hip, and distal 1/3 radius. It should be emphasized that three-site densitometry is always recommended in this disease, compared to DXA evaluation in osteoporosis where many centers perform only lumbar spine and hip BMD. The distal 1/3 site is important to examine in PHPT because classically bone disease in PHPT seems to be seen at this site first by DXA. The newest guidelines go beyond DXA and now recommend that all patients should also be screened for vertebral fractures, with either thoracolumbar spine X-rays or vertebral fracture assessment (VFA). VFA is lateral spine imaging performed at the time of DXA specifically for the purpose of fracture assessment and can reliably identify vertebral fractures [18]. Vertebral fractures are the most common fragility fractures, even in PHPT patients, and increase the risk of future fragility fractures [28]. However, because these fractures can occur without significant trauma, they are often unrecognized unless documented radiographically. Additional imaging with HRpQCT or TBS is optional, if available, but not routinely advocated.

Table 28.1 Recommended evaluation of patients with asymptomatic PHPT

Recommended evaluation of patients with asymptomatic PHPT	
Category of work up	Recommended investigation
Serum biochemistry	Serum calcium, albumin, phosphate, PTH, 25(OH)D, BUN, creatinine, alkaline phosphatase activity
Urine biochemistry	24-h urine calcium, creatinine, creatinine clearance, stone risk profile (if urine calcium >400 mg/day; >10 mmol/day)
BMD	DXA of lumbar spine, hip, and distal 1/3 radius
Spine imaging	X-ray or VFA by DXA
Abdominal imaging	X-ray, ultrasound, or CT
Genetic evaluation	If genetic cause of PHPT is suspected

Table adapted Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab 2014 Oct;99(10):3561–9

BUN blood urea nitrogen, *25(OH)D* 25-hydroxy vitamin D, *VFA* vertebral fracture assessment

Another modification to the most recent guidelines is the recommendation for routine abdominal imaging with X-ray, ultrasound, or CT to assess for asymptomatic nephrocalcinosis or kidney stones. In addition, a 24-h urine collection for calcium and creatinine is recommended to identify either significant hypercalciuria (>400 mg/day) or hypocalciuria (see FHH below). If significant hypercalciuria is found, a complete calcium-stone urinary biochemical profile should be obtained to see if an additional risk factor(s) for the development of kidney stones is present. If they are present, parathyroidectomy should be considered.

Selection of Surgical Candidates

With the most recent guidelines, surgical criteria for asymptomatic patients with PHPT have been expanded to actively screen patients for asymptomatic kidney stones, nephrocalcinosis, or those at risk for stones as evidenced by marked hypercalciuria and additional abnormalities as detected by a urinary biochemical stone profile (Table 28.2). Although a history of fragility frac-

Table 28.2 Patients with asymptomatic PHPT for whom surgery is indicated and comparison with previous guideline recommendations

Parameter	2008 Indication	2013 Indication
Serum calcium[a]	>1.0 mg/dL (>0.25 mmol/L) upper limit of normal	>1.0 mg/dL (>0.25 mmol/L) upper limit of normal
Skeletal[b]	BMD T-score < -2.5 at any site, or history of previous fragility fracture	BMD T-score <−2.5 at any site, or history of previous fragility fracture; including morphometric vertebral fractures discovered on spine imaging during initial assessment
Renal	eGFR <60 cc/min	Creatinine clearance <60 cc/min, or hypercalciuria (>400 mg/day; > 10 mmol/day) with increased urine stone risk profile, or kidney stone/nephrocalcinosis documented by abdominal X-ray, US, or CT during initial assessment
Age	<50	<50

Table adapted from Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab 2014 Oct;99(10):3561–9

[a]Calcium corrected for albumin

[b]For premenopausal women and men younger than 50, a Z-score <−2.5, rather than T-score, should be used as a surgical indication

ture has previously been a surgical indication, the addition of routine screening for morphometric vertebral fractures is likely to identify more patients.

The remaining criteria have not changed from the prior guidelines. These criteria include age <50 years, impaired renal function (creatinine clearance <60 cc/min), or BMD in the osteoporotic range (T-score <−2.5) at any of lumbar spine, hip, or distal 1/3 radius site. Age <50 years is a guideline for surgery because younger patients with PHPT develop disease progression and surgical indications more frequently than older patients during the same follow up period (23 % vs. 62 %; [29]). An important point is that patients who do not meet any guideline indications for surgery can still undergo parathyroid surgery, if this is their preference, as long as there are no medical contraindications to surgery.

Monitoring of Nonsurgical Patients

Asymptomatic patients who do not meet any surgical criteria, and chose not to have surgery, can be safely followed but require monitoring [3, 30]. Annual testing of serum calcium and creatinine clearance, as well as 3-site DXA every 1–2 years is recommended. Spine imaging should be repeated if vertebral fracture is suspected because of back pain or height loss. Similarly, symptoms of renal colic should prompt renal imaging and repeat 24-h urine collection for stone profile.

Additional Considerations

Familial Hypocalciuric Hypercalcemia (FHH)

FHH is a rare autosomal dominant condition caused by a loss-of-function mutation in the calcium-sensing receptor (CaSR) gene. The condition also presents with hypercalcemia and inappropriately normal or mildly elevated PTH. However, FHH is characterized by very low urinary calcium excretion (calcium clearance/creatinine clearance ratio <0.01) as a result of defective calcium sensing by the kidney [6]. Diagnosing FHH is important because the condition does not resolve with surgery [31]. Furthermore, no specific therapy is necessary because FHH is not usually associated with any complications in adulthood [31]. A family history of mild hypercalcemia, especially if noted in childhood, or hypercalcemia that failed to correct with parathyroidectomy, suggests FHH. A 24-h

urine calcium excretion should be measured in all patients to rule out FHH [6]. However, the fractional calcium excretion between FHH and PHPT can overlap, in which case genetic testing, which is now commercially available, is advised ([6]; Fig. 28.3).

Genetic Forms of PHPT

It is important to recognize that PHPT can occur as part of a genetic syndrome. These syndromes include multiple endocrine neoplasia (MEN) type 1 (*Menin* gene mutation), type 2A (*RET* gene mutation), and familial isolated hyperparathyroidism (FIHPT; multiple gene mutations possible) [32, 33]. Almost all patients with MEN 1 develop PHPT, generally in their 20s, and usually as the first manifestation of the syndrome [32, 33]. Subsequently patients with MEN 1 may develop functioning or nonfunctioning tumors of the pancreas and anterior pituitary, adrenal adenomas, and rarely foregut carcinoid tumors [33, 34]. Approximately 90 % of patients with MEN 2A develop medullary thyroid cancer (MTC), and this tends to be the initial presentation of the disorder [33, 34]. PHPT is found either concurrently or subsequently in 20–30 % of patients, usually after age 30 [33, 35]. Of particular significance perioperatively, half of MEN 2A patients develop pheochromocytoma [33, 34]. FIHPT is an inherited disorder of PHPT without evidence of other endocrinopathies or tumors [32]. Other genetic syndromes more rarely

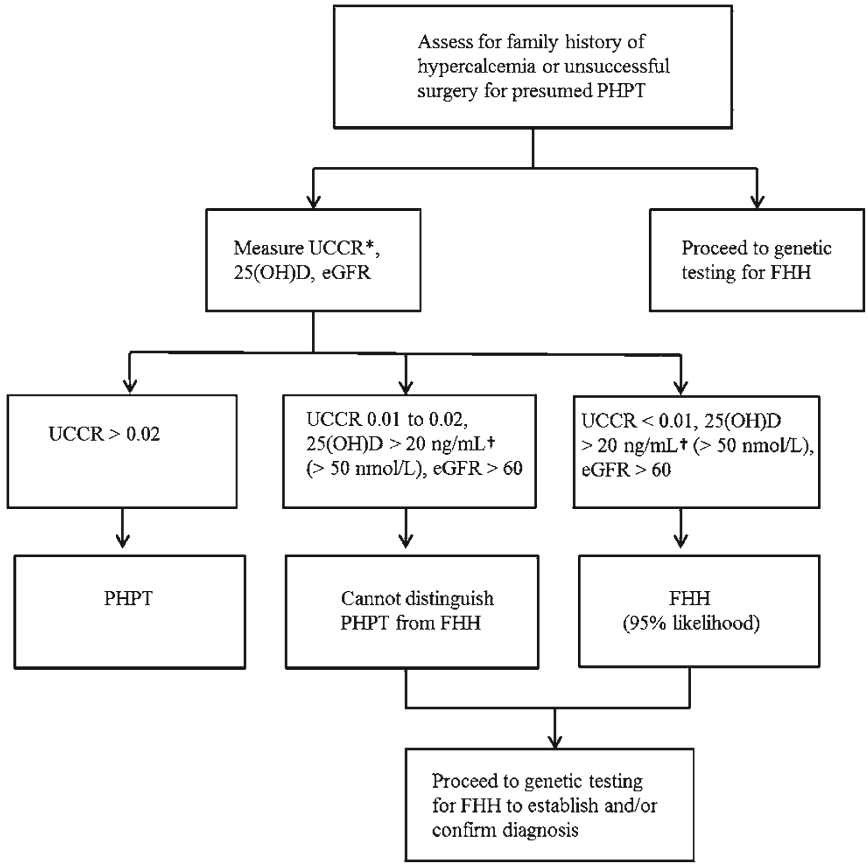

Fig. 28.3 Recommended algorithm to differentiate FHH from asymptomatic PHPT. *UCCR: urinary calcium:creatinine clearance ratio. †Vitamin D insufficiency or renal impairment may artificially lower UCCR. Figure adapted from Eastell R, Brandi ML, Costa AG, D'Amour P, Shoback DM, and Thakker RV. Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the fourth international workshop. JCEM. 2014:99(10):3570–9

associated with PHPT include MEN 2B, MEN 4, and hyperparathyroidism-jaw tumor (HPT-JT) syndrome [32, 33]. Despite the great interest in genetic etiologies of PHPT and the different genetic forms identified, all the familial hyperparathyroid syndromes together, including FHH, account for only approximately 5–10 % of all PHPT cases [9].

Since all familial hyperparathyroid syndromes have an autosomal dominant pattern of inheritance, an accurate family history is important. However, sporadic mutations can also occur making patient identification challenging [6, 33]. In addition to screening and identifying other endocrinopathies and tumors in affected patients and their family members, confirmation of a familial hyperparathyroid syndrome also influences surgical management. Many of these patients have multiglandular disease and increased rates of disease recurrence, making more extensive surgical exploration often necessary [9]. When assessing a patient with PHPT, genetic testing is indicated when: (1) the patient has a first-degree relative with known or suspected familial hyperparathyroid syndrome; (2) the patient has PHPT and another typical manifestations of a familial hyperparathyroid syndrome (ex. PHPT and MTC); (3) PHPT is diagnosed before age 45; (4) PHPT is caused by multigland disease; (5) parathyroid carcinoma or atypical adenoma is diagnosed [6, 33].

Normocalcemic PHPT (NPHPT)

NPHPT is a variant of PHPT characterized by elevated PTH concentrations with consistently normal total and ionized serum calcium, in the absence of secondary causes for an elevated PTH such as vitamin D deficiency or renal dysfunction [36]. Diagnostic criteria for NPHPT were added to the most recent guidelines and require: (1) normal serum albumin-adjusted total calcium and normal ionized calcium on several occasions; (2) confirmation of elevated PTH on at least two other occasions over 3–6 months; (3) vitamin D sufficiency (25(OH)D level at least >20 ng/mL and preferably >30 ng/mL); (4) no malabsorption syndromes such as Celiac disease; (5) normal renal function (eGFR >60 mL/min); (6) no hypercalciuria; (7) no use of medications which can raise PTH (bisphosphonates, denosumab, thiazide or loop diuretics, or lithium [6].

The natural history of NPHPT has not been fully elucidated, but it appears that some of these patients are prone to skeletal complications, kidney stones, and development of hypercalcemia [37]. Annual serum calcium and PTH monitoring and DXA every 1–2 years are recommended. There are currently no prospective studies regarding the optimal management of these patients but surgery is recommended according to the asymptomatic PHPT guidelines if hypercalcemia develops or if patients demonstrate complications of PHPT such as progressive worsening of BMD, fragility fractures, or kidney stones [3].

Nonclassical Features

Cardiovascular disease in patients with asymptomatic PHPT should not be considered an indication for parathyroid surgery, because there are limited data on effects of mild PHPT on the cardiovascular system [8]. What data are available do not clearly implicate the disease nor is it clear what aspects of subtle abnormalities discovered are reversible after successful surgery. Similarly, surgery is not routinely recommended in otherwise asymptomatic PHPT patients for nonspecific complaints such as fatigue, mood disorders, or neurocognitive complaints, because randomized controlled trials of surgery vs. observation have failed to show a consistent benefit of surgery on quality of life and psychological outcomes [8]. Further research into these areas is necessary.

Treatment Options and Outcomes

Surgery

Surgery is the only cure for PHPT. In a large cohort of patients with PHPT who underwent surgery at the Mayo Clinic, the cure rate, as defined by normocalcemia, was 97 % for the combination of conventional exploratory and minimally invasive parathyroidectomy [38].

In addition to treatment of hypercalcemia, parathyroidectomy is also associated with improved BMD. In the study of Silverberg et al., 61 surgically treated patients experienced a mean increase of 6 % in femoral neck BMD and 8 % in lumbar spine BMD by 1 year, with ongoing BMD improvement at 10 years [39] which persisted for up to 15 years [19]. Compared to baseline, BMD at the distal 1/3 radius also significantly increased following parathyroid surgery in this cohort [19], however, there was no significant difference between groups in the percent change from baseline between surgically treated and conservatively managed patients [39]. Small randomized control trials of surgery or surveillance for asymptomatic patients with PHPT also showed beneficial effect on BMD at the lumbar spine [30, 40], and total hip [40], despite enrollment of patients who did not meet surgical criteria. Most significantly, however, surgery appears to ameliorate fracture risk. In a large Danish cohort study of 3213 patients with PHPT identified from a national hospital database, the risk of hip and upper arm fracture was reduced by more than 50 % (HR 0.44 for both) in patients who had surgery compared to those who were medically managed [41]. There was no apparent reduction in forearm or spine fractures between the treatment arms. However, this observation needs to be considered in the context of an outpatient setting, where most of these fractures are treated and, therefore, may not have been captured by the database.

With regard to kidney stones, the same Danish cohort described above [42], demonstrated that the pre-intervention prevalence of stones was higher among patients who had surgery (15 % vs. 7 %), indicating these patients were more likely to be referred for, and accept surgery. Although the incidence of kidney stones decreased following surgery, it remained elevated relative to the nonsurgical cohort (9 % vs. 3 %). In the follow up period, the risk of developing kidney stones was most strongly associated with a history of prior stones (HR 8.62), emphasizing the multifactorial nature of stone formation, above and beyond hypercalcemia.

Medical Management

Bisphosphonates

Small randomized control trials suggest that alendronate therapy reduces bone resorption and increases BMD in patients with PHPT. In a 48 week trial of 40 postmenopausal women with PHPT randomized to placebo or alendronate, the intervention group showed BMD improvements of 3.8 and 4.2 % at the lumbar spine and femoral neck, respectively, compared to ongoing small losses in the placebo group [43]. Another study randomized 44 men and women with PHPT to 1 year of alendronate or placebo. Relative to baseline, in the treatment group BMD increased at the spine by 4.9 %, total hip by 4.0 %, and femoral neck by 2.1 %, whereas BMD remained stable in the control group [44]. After 1 year on placebo, the control group was crossed over to active drug and BMD increased at the spine and total hip. Distal 1/3 radius BMD remained stable in all patients regardless of initial intervention. Neither study showed a clinically significant reduction in serum calcium with alendronate treatment. Therefore, in patients with asymptomatic PHPT who are candidates for surgery based on BMD criteria but are unwilling or unable to undergo surgery, bisphosphonate therapy is a reasonable option to improve BMD and reduce fracture risk.

Calcimimetic Treatment

The utility of the calcimimetic, cinacalcet, in patients with PHPT was investigated in a 1 year randomized control trial of 78 subjects [45] followed by 4.5 year open-label extension for 45 subjects [46]. Normocalcemia was achieved in 73 % of patients treated with cinacalcet compared to 5 % treated with placebo in the original study and the mean serum calcium normalized and remained within the normal range for all subjects in the extension trial. Conversely, PTH levels remained above the normal range. Cinacalcet did not affect 24-h urine calcium excretion. During the extension trial, two patients developed kidney stones. Lumbar spine, total hip, femoral neck, and distal 1/3 radius BMD was measured annually during the entire 5.5 year study period and did not change in

response to cinacalcet treatment. Therefore, in patients with asymptomatic PHPT who would be candidates for surgery based on hypercalcemia, but are unwilling or unable to undergo surgery, cinacalcet is a reasonable therapy to achieve normocalcemia but will not improve BMD and may not protect against kidney stones.

Calcium and vitamin D

It is not necessary to limit calcium intake in patients with PHPT, unless of course calcium intake is excessive [3]. Calcium intake should follow the recommended nutritional guidelines for all adults, namely 1000–1200 mg per day. Preferably, calcium intake should be through calcium-containing foods. All patients should have measurement of 25(OH)D because vitamin D insufficiency (<20 ng/mL), or frank deficiency (<10 ng/mL) [47] may worsen PHPT by inducing a concurrent secondary increase in PTH levels. In the event of vitamin D insufficiency, supplementation with 800–1000 IU of vitamin D daily is suggested to achieve a minimum 25(OH)D level of >20 ng/mL [3]. Larger amounts may be needed, but incremental dosing of vitamin D should proceed with caution.

Summary

As the clinical phenotypes of primary hyperparathyroidism have evolved over the past 40 years, so have recommendations for its management. With greater appreciation of target organ involvement that may require more than conventional assessment of the skeleton and the kidney, it is becoming evident that even in the asymptomatic form of the disease, the most common renal and skeletal involvement can be detected with greater frequency than previously thought.

Society Guidelines: See above

Best Practices: N/A

Expert Opinion

The most recent guidelines on the management of asymptomatic PHPT are based upon evidence obtained over the past 5 years and suggest a more proactive approach to the evaluation and management of this disease.

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Osteoporosis in Primary Hyperparathyroidism: Considerations for Diagnosis and Treatment

29

Dana L. Madison

Contents

Introduction

Osteoporosis is a skeletal disorder produced by micro-architectural changes in bone structure that reduce bone mass and quality, resulting in a high risk of traumatic and nontraumatic fractures with significant morbidity and mortality.

Primary Hyperparathyroidism (PHPT) has variable effects on the skeleton depending on disease severity and time present. The impact on skeletal health is a critical component for determining therapy in both surgical and nonsurgical patients. Understanding the prevalence and risk factors for this often under-diagnosed, silent disease are necessary for effective and appropriate PHPT management.

Clinical Presentation and Prevalence

Osteoporosis Is an Under-Recognized Health Problem

Osteoporotic fragility fractures are responsible for a significant worldwide percentage of disability adjusted life-years including escalating morbidity, mortality, and health care costs [1]. Epidemiological studies suggest that 30 % of all postmenopausal women have osteoporosis and that 40 % of these women and up to 15–30 % of all men age >50

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years will sustain a fragility fracture [2]. Statistically, osteoporotic fractures are more prevalent than many cancers including breast cancer and cause complications such as increased hospital stays at a rate greater than diabetes and acute myocardial infarction [3]. The high prevalence of under- and nondiagnosed patients, relative undertreatment, and poor outcomes demonstrates that proper assessment for bone loss and fracture risks are necessary in PHPT patients who have additional bone loss risks.

The incidence of osteoporosis and its projected health care costs are significant. It is estimated that greater than 9 million new fragility fractures occur each year. By 2050 the incidence of hip fracture is projected to increase 310 % in men and 240 % in women [4], affecting at least 10 % of women age 60 years. Osteoporotic fractures occur at the spine > hip > distal forearm, with spine and hip fractures increasing overall mortality and forearm fractures leading to decreased mobility and function for more than 6 months. At least 33 % of women and 20 % of men age >50 will experience an osteoporotic fracture with a combined lifetime risk nearing 40 %, the same as for cardiovascular disease [5]. Women incur the majority of the fractures compared with men, having a lifetime fracture risk of 40–50 % in women and 13–22 % in men [6]. Long-term morbidity with some form of disability is estimated at 7–13 % [7]. Additionally, some analyses find a mortality rate of 8 % in men and 3 % of women (US) within 6 months of an acute hip fracture [8], that rise to 24 % in women and 26 % in men after 5 years [9].

Many of these first fractures are the initial incident where osteoporosis is recognized. Clinicians evaluating for PHPT need to be aware of the high osteoporosis disease prevalence since preexisting osteoporosis is an important consideration for both surgical recommendations and medical therapy.

Definition and Measurement of Osteoporosis

The World Health Organization (WHO) defines osteoporosis in postmenopausal women and men as a total hip Bone Mineral Density (BMD) measurement ≤−2.5 Standard Deviations (sd) below the population mean for young healthy adults [10]. BMD is commonly measured by Dual-energy X-ray Absorptiometry (DXA), which are 2-dimensional images measuring areal BMD (g/cm^2) dependent on bone size. Although widely accepted and incorporated into the WHO consensus definition, BMD has both advantages and certain clinically relevant limitations.

Clinical advantages of DXA are the ability to predict fracture risks and monitor response to therapy. Relevant limitations of DXA are the measurement errors (accuracy) produced by bone shape and soft tissue heterogeneity, whereas precision errors (reproducibility) have lower variability when serial studies are performed on the same instrument. Inter-instrument comparison and calculation of statistical change is usually not as robust as intra-instrument precision, owing to the unique calibration of each individual instrument [11]; therefore, analyzing statistically significant changes over time between studies requires each be performed on the same instrument.

Bone density measurements are performed at the total hip, femoral neck, and spine. Additionally, measurement of cortical BMD at the 33 % distal radius site is a valid method for assessing BMD in PHPT patients, but also in those who have either discordant hip and spine measurements or have confounding elements at those sites (e.g., extravertebral osteophytes, bilateral hip replacement). These measurements determine a patient's relative standard deviation to the population mean using the appropriate database for either a young healthy adult mean or an age matched mean. These standard deviations are t-scores when relative to the young adult mean, z-scores when relative to the patient's age matched mean. These values determine either low bone mass from −1 to −2.5 standard deviations (osteopenia) or osteoporosis using the WHO t-score definition for osteoporosis as less than −2.5 standard deviations below the healthy young adult mean. A patient's t-score is used clinically for: (1) a statistical prediction of fracture risk, (2) in the FRAX (WHO Fracture Risk Assessment Tool; http://www.shef.ac.uk/FRAX) fracture risk factor calculator and (3) in monitoring treatment response [10, 12–14].

Specifically, t-scores reflect the difference between a patient's measured BMD and the young adult healthy mean BMD (age, gender, ethnicity matched) divided by the Young adult population standard deviation.

$$\text{t-score} = [\text{Measured BMD} - \text{Mean BMD (young adult)}]/\text{Young Adult population sd}$$

The Z-score uses the same equation, substituting in the age matched mean BMD and population standard deviation, instead of the young adult mean. Z-scores can be useful in patient's age less than the osteoporosis-defined age of 50 or in growing children. By definition, a t-score of −2.5 at any site indicates osteoporosis (Table 29.1) and a z-score <−2.0 is lower than the expected range for an appropriate reference group.

Bone density measurements can be a powerful tool for determining who may be at risk for fracture. Since the evaluation is based on a population risk model in which the fracture and nonfracture groups overlap at certain levels of bone density, it is important to remember that large epidemiologic trials have determined that the overall risk increases exponentially for progressively lower BMD [15, 16]. Conversely, a minimally low bone mass (t-score between −1 and −2.5) does not absolve nor reduce the patient from fracture risk if certain clinical elements exist(ed) either in their bone formative years or in the pre-aging skeleton before age 50. To illustrate this point, the majority of osteoporotic fractures occur with a T score greater than −2.5 [17]. Clinicians should be aware that osteoporosis and fracture risks are multifactorial and any additive risks culminating in small changes in bone density may translate into much larger fracture risks. This fact is more evident at older ages where fracture risks rise significantly for small changes in BMD at any absolute density. Effective assessment can identify patients needing treatment and in whom the presence of osteoporosis and/or higher than age normal fracture risk may change the treatment recommendations during a PHPT evaluation.

Table 29.1 Diagnostic criteria by t-score for osteoporosis, low bone mass or normal bone mass

t-score	Bone mass
0 to –1	Normal
–1 to –2.5	Low bone mass
<–2.5	Osteoporosis

Pathophysiology of Osteoporosis

Osteoporosis is a disease of structural fragility produced by functional differences in bone formation, resorption, and repair. Primary osteoporosis is a multifactorial and not well-understood multi-pathway process leading to low bone mass and increased fracture risks in the aging skeleton. Secondary osteoporosis occurs when clinical events or diseases lead to an increased fracture risk.

In general terms, the pathophysiology of osteoporosis is grouped into three functional categories:

1. Failure to attain an optimized mean peak bone mass and quality,
2. Accelerated bone loss from increases in resorption, and
3. A decrease in bone formation during remodeling and repair.

Aging impacts all these mechanisms including an increase in falls and physical events that increase fracture risk.

Genetic determinants for skeletal strength, bone mass, bone maintenance, and fracture risk are known, but their overall respective contributions are still under active investigation [18]. In addition to genetic factors, the most common physiologic changes leading to increased fracture risk center on nutritional factors and sex steroids. A healthy skeleton is one that attains its genetically maximal peak bone mass and minimizes the effects of aging on bone loss. Maximizing peak bone mass is achieved through genetic determinants, nutritional access (including calcium, Vitamin D3, and good protein calorie nutrition), normal puberty and sex steroid maturation, normal thyroid and pituitary function, body habitus, and physical activity [19]. Preventing premature loss or accelerated age-related loss is achieved through avoiding severe illness, nutritional deficits, lifelong low Vitamin D3 and calcium intake, early

changes in sex steroids (particularly estrogen for women), and certain medications, principally glucocorticoids. The interplay of these factors allows low bone mass, early osteoporosis, or accelerated bone loss to occur in any aging patient or in younger patients age less than 50 years.

Postmenopausal osteoporosis is defined as a state of increased bone turnover and lesser effective remodeling and bone deposition; however, a high turnover state is not the only pathophysiological risk for lower bone mass and / or fracture risk in all patients with low bone mass. For example, high bone turnover is present in adolescents and is not equated with elevated fracture risk; therefore, there must be other elements to consider in assessing for fracture risk and the structural changes that lead to a decrease in first microscopic bone stability and strength, followed by macroscopic structural failure and fracture. Various developmental influences, protracted clinical states (e.g., primary or secondary amenorrhea, anorexia) or repetitive use of glucocorticoids in the skeletal growth years may decrease the attainment of maximal peak bone mass. Later in life this may lead to an increased risk of fracture and higher rate of osteoporosis owing to a lower starting bone density from which age-related loss begins and an overall lessening of bone quality. Chronic diseases such as diabetes may also directly impact bone quality without an effect on bone density accounting for a higher fracture rate in diabetics [14]. Additionally, age itself independent of bone mass density is a fracture risk predictor. For example, at the same BMD (e.g., t-score −3 femoral neck), in someone at age 80 there is a sixfold higher risk of fracture as compared to age 50 [20]. These observations suggest that bone quality is important and understanding the effects of various positive and negative elements on bone will impact clinical decisions.

A primary example of these differences exists in patients age <50 years who could have an equivalent fracture risk in the correct setting as compared to an older patient. For example, the addition of PHPT can be a singular tipping point in a younger patient that significantly raises their risk of fracture if they possess other low bone mass risk factors. Similarly, long standing mild PHPT in an older patient also may negate years of positive bone building effects and minimal age-related bone loss prior to PHPT onset. The FRAX algorithm [13] attempts to fuse these ideas towards a more inclusive risk assessment by using a complete clinical evaluation and BMD. FRAX uses a risk factor based algorithm, incorporating the risk of fracture and death from a number of prominent bone loss risks and conditions of secondary osteoporosis. The risk result is a 10-year probability of major osteoporotic fracture (spine, hip, humerus, wrist) or hip fracture alone. The National Osteoporosis Foundation (NOF) has recently adopted FRAX to their recommendations for treatment criteria with a fracture risk threshold of 3% for hip fracture and 20% risk for an osteoporotic fracture at any site [21]. Other countries and associations now include FRAX in their respective guidelines, although debate is ongoing at where a uniform intervention threshold will lie. Similar to BMD measurements alone, FRAX has limitations and cannot be used to judge response to therapy. One relevant limitation is that presence of concomitant PHPT is not included in the FRAX analysis since PHPT confers a variable risk for BMD reduction in individual patients. There is currently no predictive algorithm that accurately determines the bone loss rate or additive fracture risk in a PHPT patient. A bone quality assessment may be relevant in future work, since at a given BMD a PHPT patient with a low bone mass BMD may have more fracture risk than a BMD matched, non-PHPT patient. Using all of these tools, BMD, FRAX, and a comprehensive clinical assessment of risk factors for low bone mass and accelerated bone loss is the most complete way to determine fracture risk in an individual patient.

Therapy for Osteoporosis

Treating osteoporosis relies on identifying and modifying bone loss risk factors, supplying adequate material for new bone synthesis and using pharmacologic modifications of the bone remodeling cycle where indicated. Importantly, the risk and impact of falls must be addressed.

At any clinical assessment for osteoporosis and in particular for the aging patient, identifying

daily risk factors for falls is critical. Modifying the home environment as well as strengthening, conditioning, agility, and muscle training are all factors that are often overlooked as elements that can prevent fragility fracture by averting the actual physical event that precipitates the fracture. Data from athletes, astronauts, and older adults in strengthening programs have all demonstrated there can be anatomic specific and global bone mass reductions from loss of use and gains from strengthening programs [22, 23].

Calcium and Vitamin D3

Metabolic and nutritional therapy is required for adequate bone formation during remodeling. Calcium and Vitamin D3 are necessary for this process and often inadequately acquired in the diet and poorly absorbed as people age. Calcium is absorbed minimally and passively in the small intestine (~20 % of a calcium load, limited efficiency past 500 mg) [24]. Active absorption up to ~80 % of a calcium load occurs in the presence of adequate activated Vitamin D3 [1,25$(OH)_2$D3]. Calcium homeostasis is maintained through the activity of Parathyroid Hormone (PTH) and its actions on the kidney (active calcium reabsorption), skeleton, and the enzyme 1-alpha hydroxylase that synthesizes 1,25$(OH)_2$D3 from its storage form, 25(OH)D3. Serum Vitamin D3 levels decline with aging, season, darker skin pigment and nutritional access. PTH and serum 25(OH)D3 are inversely proportionate in order to maintain serum calcium levels within a relatively narrow range. Inadequate intake of Vitamin D3 and or calcium leads to relative deficiencies and a decline in serum calcium with an appropriate, compensatory elevation in PTH. The PTH rise increases bone remodeling, calcium reentry from the renal filtrate and synthesis of activated Vitamin D3 (1,25$(OH)_2$D3) all to maintain serum calcium levels. Protracted deficiencies in calcium and Vitamin D3 produce chronic secondary HPT, a high bone turnover state that leads to accelerated bone loss, declining bone density, and bone quality thereby increasing the fracture risk. Access to adequate calcium intake of ~1000 mg elemental calcium per day can lower the remodeling rates ~20 % and increase BMD within 12–18 months [25]. Achieving Vitamin D3 sufficiency with adequate calcium intake will revert secondary HPT, lowering the PTH and decrease or revert the negative bone effects. Since calcium and Vitamin D3 insufficiency are very common in osteoporosis patients, these deficiencies must first be corrected before other therapies are used.

Currently, there is debate about calcium and Vitamin D3 supplementation in the general population and these data are beyond the scope of this Chapter to review; however, it is important to recognize that in at risk populations there is good quality data showing bone mineral density gains [26] and vertebral but not nonvertebral fracture risk reduction [27] for calcium supplementation and both vertebral and nonvertebral fracture reduction with dose-dependent Vitamin D3 supplementation [28]. Recommendations for supplementation, daily intake, and therapeutic use vary significantly depending on the country and recommending group. In osteoporosis and older patients it is important to remember that adequacy is not often judged by the dose given based on generalized recommendations, but by effective absorption in each individual since these patients have an underlying disorder that by its nature requires adequate calcium and Vitamin D3 to revert increased bone loss. Nutritional adequacy for osteoporosis treatment with calcium and Vitamin D3 is often judged by measuring Vitamin D3 [25(OH)D3] levels and assessing calcium sufficiency by PTH and 24-h urine calcium measurements following normal Vitamin D3 levels (30 ng/mL; 75 nmol/L). Recommendations will vary, but on average osteoporotic patients require 800–1200 mg elemental calcium given in divided doses daily with a dose of Vitamin D3 necessary to achieve sufficiency.

Osteoporosis Pharmacotherapeutics

Pharmacologic therapy for osteoporosis centers on first establishing good calcium and Vitamin D3 use, correcting underlying deficiencies and secondary HPT and then using one of the available agents such as Bisphosphonates (e.g.,

Alendronate), estrogens, or Selective Receptor Estrogen Receptor Modulators (SERMs) (e.g., Raloxifene), inhibitors of the activator of nuclear factor kB ligand (RANKL) (Denosumab), recombinant PTH (Teriparatide), or calcitonin.

In aging women, as sex steroid levels decline in the peri-menopasuse into menopause for the first few years there is an accelerated rate of bone loss followed by a relatively constant, downward sloping loss. The use of postmenopausal estrogen, with the controversies surrounding its non-skeletal positive and negative effects is beyond the scope of this chapter. Historically, estrogen is known to improve bone density and reduce the risk of vertebral and nonvertebral fractures, but the effect lasts for only as long as estrogen is being used and BMD declines up to 5 % in the first year following cessation, mirroring the rate of early menopausal bone loss [29]. In general estrogen is not recommended as a primary therapy for prevention or treatment of osteoporosis, but will provide positive effects in those taking it for relief of postmenopausal symptoms.

Selective Receptor Estrogen Receptor Modulators such as Raloxifene have a significant reduction on vertebral but not nonvertebral fractures. Raloxifene decreased the risk of invasive breast cancer by 76 % [30], and in osteopenic patients Raloxifene can be used to prevent bone loss; however, the lack of efficacy at nonvertebral sites, other safety and long-term efficacy issues and failed clinical trials on newer molecules have reduced the use and recommendation for the use of SERMs.

Bisphosphonates are a mainstay of osteoporosis therapy and can reduce vertebral fractures 35–65 % and nonvertebral fractures on average 20–25 % [31]. These reductions are seen after 2–3 years with correspondingly smaller gains in BMD, again highlighting the exponential effects of small bone density changes that correspond to large reductions in fracture risk. Different levels of effect have been seen in trials with the different drugs including the intravenous (Zoledronate) versus weekly (Alendronate) and monthly (Risedronate) oral preparations (Alendronate, Risedronate), but all significantly lower fracture risks. Length of therapy, combining different pharmacological agents with bisphosphonates, and protection from fracture after stopping therapy all have multifactorial confounders, but a starting BMD t-score <–2.5 in a higher risk, fracture naïve patient, appears to gain the most benefit from more prolonged therapy [32, 33].

Denosumab is a novel monoclonal antibody directed against RANKL. The balance between RANKL and osteoprotegrin as influenced by PTH, estrogens, and glucocorticoids can modify osteoclastic activation and therefore bone resorption. Various animal models and human genetic polymorphisms or deficiencies in parts of this system have shown inhibiting RANKL can lead to increases in bone formation and decreases in bone resorption [34]. In clinical trials Denosumab increases bone density on average at the spine 6.5 % and total hip 2.4 % over 2 years [35] while the largest trial to date powered for fracture shows relative risk reductions of 68 % spine, 20 % nonvertebral and 63 % hip [36]. Long-term use of Denosumab is still being evaluated, but cessation of therapy appears to return the bone turnover state to prior physiology, similar to stopping estrogen and different from bisphosphonates which have longer lasting effects on bone remodeling [37]. Unlike bisphosphonates, Denosumab can be used in patients with renal failure, and has proven to be particularly useful in treating osteoporosis in the elderly with impaired renal function.

Long-term safety, rare to very rare side effects including osteonecrosis of the jaw and atypical subtrochanteric fractures, use and monitoring concerns have received recent attention. The analysis of large-scale trials and epidemiology on these issues has shown these concerning side effects are very rare for bisphosphonates or Denosumab. A position statement and detailed analysis of the literature has been issued by the American Society for Bone and Mineral Research (ASBMR) and was recently updated [38]. Overall the use of these medications is an important part of overall osteoporosis therapy in reducing fracture risk and morbidity and mortality and the presence of these is exceedingly rare side effects does not compromise their known benefits.

Recombinant PTH (rPTH; Teriparatide) is an anabolic therapy providing larger incremental

gains in bone density at the spine than other pharmacologic compounds. PTH may stimulate both bone formation initially and then resorption and formation simultaneously. The pharmacologic effect by pulsatile administration (daily injection) differs physiologically for its effect on bone than a continual elevation in PHPT or secondary HPT from Vitamin D3 deficiency, both of which lead to higher bone turnover and bone density reduction. Current therapeutic use is time limited because of an increase in osteosarcoma in rats during evaluation, but significant gains in vertebral (13.7 %) and femoral neck (6 %) BMD occurred with loss at the radius (2–4 %) over 18 months [39]. Vertebral fractures were reduced 69 % and nonvertebral fractures 54 %. Despite the decrease in BMD at the radius there was also a nonstatistical significant trend in fracture reduction at the wrist. Bone density gains are lost 12–18 months after cessation of rPTH but are maintained if treatment is followed with an antiresorptive agent [40]. Use of Teriparatide in combination therapy and for other indications is under active consideration. Teriparatide is contraindicated in PHPT, Paget's disease, disorders of high bone turnover or risk of osteosarcoma (prior radiation exposure) and unexplained alkaline phosphatase elevations.

Calcitonin has been examined for its use on osteoporosis but its efficacy on bone turnover, bone density gains, and fracture reduction has been mixed to minimal to none; therefore, Calcitonin is not usually considered amongst the typical therapeutic choices.

Practical Considerations of Osteoporosis in Primary Hyperparathyroidism Patients

Primary Hyperparathyroidism produces a generally asymptomatic hypercalcemia, predominately from a single gland adenoma. There is a wide range of clinical presentation, but in general a less severe pathologic presentation exists than in the past, likely due to shortened time of disease before discovery. PHPT in past years and currently in certain patient populations still can present with pathologic fractures and severe skeletal changes such as osteitis fibrosa cystica. Other chapters in this book have extensively assessed the specific evaluation, treatment and long, and short-term sequelae of PHPT. How PHPT patients should be assessed and treated for osteoporosis is an important part of their comprehensive care.

The decline of severe PHPT in North America and Europe does not mean the skeletal risk is lessened for patients with long-present disease or additive bone mass loss risks. Undiagnosed low bone mass or osteoporosis in the PHPT patient factors into both surgical decision making and medical management pre and post-parathyroidectomy. The impact on bone health varies, depending on whether the patient is to be treated surgically and potentially cured or followed medically. In medical observation, patients have the potential for further bone loss and an increased fracture risk from both the PHPT and any additional osteoporosis risk factors. Some studies suggest that all cause mortality in PHPT is increased during long-term observation past a certain threshold of years; however, these studies are not powered to look at an increase in fracture [41, 42]. Determining skeletal risk should occur at the initial evaluation and raises two important clinical questions.

1. What is the patient's underlying skeletal health status and do they have low bone mass or osteoporosis?
2. How does a patient's BMD and fracture risks affect the recommendation for surgical correction or medical management?

What Is the Patient's Underlying Skeletal Health Status and Do They Have Low Bone Mass or Osteoporosis?

The aging patient of both genders (age >50 years) is at risk for osteoporosis and fracture. Patients at any age may also be at risk for secondary osteoporosis if certain medical conditions and/or therapies have occurred. Coincident clinical conditions may also lead to a blunting of osteoporosis therapy and exac-

erbate underlying bone loss. PHPT is a high bone turnover state and therefore increases the risk of fracture by decreasing the micro-architecture stability and bone quality [43]. Cortical bone loss occurs predominately at the distal 1/3 radius, although recent evidence suggests previously unrecognized trabecular bone loss and qualitative changes at the spine and hip also increase fracture risk at these sites. Since osteoporosis is common in older patients, coincident presentation is likely and therefore a complete bone loss risk evaluation should be completed on each PHPT patient age>50 and on appropriate younger patients in whom there may be a risk for reduction in bone quality and therefore a lower than expected age-related BMD.

Secondary osteoporosis is present in 30–50 % of pre and postmenopausal women and 50–80 % of men with factors that are detrimental to skeletal health [44]. Common risk factors leading to either accelerated bone loss or decreased bone formation with a decrease in skeletal strength are shown in Table 29.2. Among these are conditions that may affect adequate nutrition (celiac disease), changes in bone turnover (hyperparathyroidism), disorders of mineral homeostasis (primary hypercalciuria), medications that affect bone either directly or indirectly (glucocorticoids, anti-convulsants), and disorders of bone marrow (multiple myeloma). Some of these events may have influenced a patient's maximal bone mass attainment in their formative years resulting in a lower peak bone mass. These patients have less tolerable cumulative loss before reaching a point of increased fracture risk and/or osteoporosis much earlier than their peers, even in their early 40's. Many of these risks are indications for a BMD at an early age, but often those are not completed except in specific situations where governing bodies have recommended the test as standard of care (e.g., transplant patients, severe asthma using glucocorticoids). Additionally, younger PHPT patients (< age 40) can have the disorder for many years before it is identified with the potential for early bone loss. All of these populations warrant an increased attention to their skeletal loss and fracture risks at the initial evaluation for PHPT and prior to surgical correction.

Table 29.2 Common clinical conditions assocaited with either accelerated bone loss or decreased bone mass attainment leading to Secondary Osteoporosis

Factors Associated with Secondary Osteoporosis
Endocrine Disorders
Hypogonadism
Hyperthyroidism
Primary Hyperparathyroidism
Vitamin D insufficiency/deficiency (secondary HPT)
Cushing's Disease
Phosphate or Calcium wasting
Gastrointestinal disorders
Malabsorption (celiac disease, IBD)
Cirrhosis, poor nutrition
Eating disorders in younger patients
Bone marrow disorders
Leukemia and lymphoma
Multiple myeloma
Connective tissue disorders
Rheumatoid arthritis
Renal disorders
Hypercalciuria
Medications associated with low bone mass
Anti-epileptics (many)
Aromatase inhibitors (breast cancer)
Chemotherapy/immunosuppressive agents
Corticosteroids
Excess thyroid hormone
Gonadotropin-releasing hormone agonists
Heparin

A BMD measurement is recommended for the initial evaluation in all PHPT patients [45–47]; however, some studies show these are not routinely performed in preoperative assessments [48]. In some patients, a disparately low radial BMD compared to the hip and spine may be an indicator that the disease has been present longer than suspected. One might see this in pre-menopausal women where estrogen is more protective at the hip and spine. Finding a t-score <−2.5 at any site in a patient age >50 years is an indication for surgery. If the patient is <50 years old, then a Z-score determination should be made and if <−2.5 this is also an indication for surgery. Using Z-scores in the age <50 years population of PHPT patients is indicated and consistent

with the positions of governing bodies on interpretation of BMD in younger patients [49].

The complete medical evaluation of skeletal health as part of the recommended workup for PHPT is covered extensively in other Chapters. The skeletal portion of those recommendations includes the following:

1. A full medical history looking for reasons for early bone loss, early formative years bone qualitative changes or reasons for poor bone formation prior to age 50.
2. Additional risk factor analysis including family history of osteoporosis, hypercalcemia, PHPT, nephrolithiasis, or other metabolic bone disorders.
3. Biochemical workup including serum total and ionized calcium, albumin, phosphorous, magnesium, PTH, 25(OH)D3, alkaline phosphatase, creatinine, urine calcium, and creatinine with calculated Ca/Cr.
4. A 3 site BMD (spine, hip, and distal 1/3 radius) by DXA.
5. Vertebral fracture assessment by X-ray.

How Does a Patient's BMD and Fracture Risks Affect the Recommendation for Surgical Correction or Medical Management?

Increased bone turnover in PHPT does not have a direct, clear association with increased fracture rates because of confounding and coexisting bone loss, low bone mass, and osteoporosis. In classical, severe PHPT the fracture rates are elevated [50, 51]. Some cohorts show differences in both increased vertebral and nonvertebral fractures [52], despite lesser degrees of bone loss at the trabecular sites. Some studies have shown a very high prevalence (~44 %) of vertebral fractures that were both silent and asymptomatic, even in mild PHPT [53]. A recent single center analysis of consecutive patients showed a 34 % prevalence of vertebral fractures, ~10 % nonvertebral fractures with a 60 % prevalence of osteoporosis [54]. If any PHPT patient has additional osteoporosis risk factors, or if significantly low spine or hip BMD is found in a newly diagnosed PHPT patient, then there may be a previously unrecognized, considerably increased fracture risk. Recent guidelines revisited this issue and recommend routine screening for fractures in addition to BMD [45]. If the prevalence of silent fracture data [54] are widely applicable in other centers, then this observation lends power to the recommendation in those patients who might be considered nonsurgical that screening for occult fracture by X-ray may essentially "restage" the patients' long-term fracture risk and change the recommendations for surgical correction and medical management. Since a known fracture is part of the surgical criteria and if the prevalence is truly higher than previously suspected, a screening lumbar spine X-ray becomes as important as the BMD since these data suggest routine screening would both increase the number of patients identified as surgical candidates and accelerate the medical management of an otherwise unknown fragility fracture.

If more routine screening for occult fracture increases the number of surgical patients this raises an interesting question: should we narrow the definition of patients who can be observed medically as only those with minimal hypercalcemia, no evidence of nephrolithiasis, a normal or minimally low bone mass BMD without evidence of accelerated loss and no radiographic evidence of fracture? If well powered studies show either a higher prevalence of fracture at initial assessment or a higher risk during a defined observation period for a given starting BMD, then both screening for fracture and a projected risk based on age, BMD, and loss rate are necessary tools for choosing surgical patients. These are valuable issues to consider in the context of the question should everyone with PHPT be offered surgery. An increase in the "at risk" population based on these observations may increase recommendations for surgery in more PHPT patients with an identifiable lesion and acceptable surgical risks, as compared with patients

for medical observation. How these risk factors set the two groups apart and what can be done to reduce the bone loss and fracture risks in medically managed patients are ongoing issues that require additional well-powered, longitudinal studies.

How does parathyroidectomy affect bone density and fracture risk? Studies comparing parathyroidectomy and observation demonstrated significant BMD increases in both male/pre-menopausal female patients or postmenopausal women within 1–8 years, with the greatest increases at the lumbar spine and femoral neck while variable gains were noted at the distal 1/3 radius [55–57]. In one cohort, bone density improved 8.2 % (Lumbar spine), 12.7 % (Femoral neck) and 4 % (Radius) after 4 years, except in postmenopausal women who gained 12.5 % at the Lumbar spine. Further analysis in a similar cohort showed rapid increases after 1 year (Lumbar spine, 8 %; Femoral neck, 6 %; Radius, not significant) and sustained increases at a lower rate through 10 years (Lumbar spine 12 %, Femoral neck, 14 %) [58, 59]. Other groups have noted similar gains in genetically different cohorts. A Japanese study reported a significant 15 % increase at the Lumbar spine and 23 % gain at the distal 1/3 radius in male and pre-menopausal female patients, with similar numbers in postmenopausal women [60]. The Mayo cohort demonstrated in 420 consecutive patients that ~75 % had bone density gains following parathyroidectomy, with 31 % having a >5 % BMD gain at the most affected (lowest t-score) site 36 months following parathyroidectomy [61]. The data on fracture risk reduction after parathyroidectomy are limited. A 5-year follow up study showed decreases in femoral neck BMD in nonsurgical patients and significant gains in vertebral and nonvertebral BMD in parathyroidectomy patients [62]. Interestingly, they found 8.5 % had undiagnosed vertebral fractures at baseline evaluation and 9 % new fractures in the nonsurgically treated patients after 5 years. No new fractures were found in the surgically treated patients, but the total number of fractures (5 individual patients) is not statistically significant because of both time and total patient number. Two other studies showing improvement of BMD following surgical correction also suggested an improvement in fracture incidence [63, 64]. The current view is that surgical correction of PHPT improves BMD and potentially forestalls additive fracture risks at all sites compared to medical observation. Further work to identify at risk patients or expand the group of patients in whom surgical correction is recommended to improve long-term bone loss and fracture risks will likely expand the surgical inclusion criteria.

How does medical therapy form an adjunct to pre-and postoperative care in PHPT patients? Medical management can be done safely in some asymptomatic patients and in those where surgery is contraindicated, declined, or has failed to correct the hypercalcemia. After surgery care may focus on treating osteoporosis, improving bone mass in non-osteoporotic patients and reducing long-term fracture risks. If there are truly unrecognized qualitative bone changes in PHPT patients at any given bone density that increase fracture risk as compared to BMD matched non-PHPT patients, then there may be reasons to treat these patients more aggressively following Parathyroidectomy. Further longitudinal studies examining indices of bone quality, bone density, and fracture rates are needed to answer this question.

For patients in whom parathyroidectomy is not performed, monitoring focuses on the plasma calcium level and minimizing skeletal and renal complications. Current recommendations suggest a serum calcium, PTH and 25(OH) D3 annually, and a BMD every 1–2 years depending on the clinical severity or suspicion for bone loss [65, 66].

Vitamin D3 can usually be replenished safely to a level of 30 ng/dL (75 nmol/L), although individual exceptions exist. Repleting Vitamin D3 may decrease PTH levels and improve bone density; however, in some studies this also increases hypercalciuria without an increase in kidney stone formation [67]. Some studies demonstrate safe use of Vitamin D3 either preoperatively or for long-term management and may

include some modest gains in bone density [67], but without benefit in other subjective indices [68]. Preoperative correction of Vitamin D3 levels is also sometimes sought to decrease the incidence of postoperative hypocalcemia and hungry bone syndrome. Current recommendations suggest careful replenishment towards 30 ng/dL (75 nmol/L) with supplemental doses (not large pharmacologic doses) that may have more positive than deleterious effects, but also recognizing that the available studies are prospectively limiting [66].

Estrogen therapy in postmenopausal PHPT patients may reduce bone resorption and improve BMD. These limited studies do not provide fracture data but the relative risks of using estrogen in individual patients needs to be balanced against these limited studies. No conclusions or recommendations have been made specifically suggesting estrogen as medical therapy in PHPT. Similarly, Raloxifene studies in PHPT patients are very limited and no conclusions can be drawn on its use in PHPT.

Bisphosphonates are better studied with Alendronate being the most evaluated drug in both men and postmenopausal women. Other bisphosphonates and Denosumab have little to no data on their use in PHPT patients while Teriparatide (rPTH) is contra-indicated in hypercalcemia/PHPT. In PHPT patients, Alendronate increases BMD at both the hip and spine up to 6 % without significant changes in serum calcium, PTH or urinary calcium excretion [67–69]. There are no fracture data from these studies so long-term effects in medically treated patients are not known. Similarly, there are no direct comparative studies examining postsurgical care using bisphosphonates so the answers to if they should be used, when to start the drug and should PHPT patients at any given BMD be considered a qualitative bone loss risk and therefore treated if they do not gain BMD following surgery, remain open questions. For nonsurgical patients Alendronate can provide positive skeletal changes and is therefore recommended in at risk patients.

The use of Cinacalet in patients with PHPT and severe hypercalcemia who are unable to undergo surgery is now approved; however, there is no data on fracture prevention and the little data on bone density suggests no significant positive effects [70]. The use of Cinacalcet in PHPT is described in detail in other chapters.

Summary

Osteoporosis is an under-diagnosed disease with high prevalence. In PHPT patients, the presence of low bone mass or osteoporosis constitutes an additive risk for accelerated bone loss and therefore increased risk of fracture. Determining a patients fracture and bone mass loss risk factors is part of a complete clinical evaluation to decide on comprehensive medical and surgical therapy in PHPT patients. Recognition of osteoporosis or the risks for developing osteoporosis in PHPT is necessary for early intervention and may also contribute to expanded surgical inclusion criteria in the future. Postsurgical medical therapy for bone health is necessary for managing fracture risk factors in the aging skeleton and reversing the negative influence of PHPT in all patients.

Clinicians treating PHPT in patients of all age groups must be aware of the additional risks presented by this disease for bone loss and therefore risk of a fragility fracture. Bone quality and bone density both play a significant role and therefore patients younger than age 50 may still be at risk from these issues necessitating that all PHPT patients undergo bone loss and fracture risk screening. Current guidelines recommend bone density testing in all PHPT patients and have added screening for occult fracture as a new point that may increase the number of patients recommended for surgical correction. Care of life-long bone risks following surgical correction including medical therapy for at risk bone densities or newly discovered osteoporosis will decrease the overall incidence of fractures and its inherent morbidity and mortality. Below is a summary of the major points of this Chapter including salient recommendations from the Fourth International Workshop on hyperparathyroidism.

Society Guidelines

From the Fourth International Workshop on hyperparathyroidism salient recommendations for bone health in PHPT.

1. All PHPT patients should have a medical bone loss risk assessment and screening for low bone mass and osteoporosis that includes medical history, laboratory evaluation.
2. All PHPT patients should have a 3 site BMD (spine, hip, distal 1/3 radius).
3. The presence of a T-score <−2.5 (age >50 years) or a Z-score <−2.5 (age <50 years) is an indication for surgery.
4. There may be benefit to screening all PHPT patients with lumbar spine X-rays for occult vertebral fracture. Current guidelines have added X-ray of the spine to the "recommended" assessment given the suggestion of a higher than suspected prevalence of occult vertebral fractures.
5. The presence of a new or undocumented vertebral fragility fracture is an indication for surgery at any given bone density.

Best Practices

For patients undergoing surgical correction or those who do not meet criteria for parathyroidectomy their short and long-term bone loss and fracture risks must be managed life-long.

1. Following Parathyroidectomy, there should be continued medical management of bone loss risks and treatment of increased fracture risks. A potential decrease in bone quality from PHPT despite a "lower-risk" (more normal) BMD still may constitute an unrealized increased fracture risk.
2. Medical therapy including the use of calcium and Vitamin D3 can be used with caution and monitoring.
3. Alendronate provides positive skeletal effects in appropriately screened and selected, nonsurgical patients and its use is recommended for reduction in bone mass density loss; there are no specific data on fracture risk reduction.
4. Medically managed patients should have routine biochemical and BMD screening to look for development of surgical criteria or the need for further intervention in those who are unable to undergo surgery.

Expert Opinion

Osteoporosis has a near silent presentation in many patients. Hyperparathyroidism will accelerate bone loss and increase fracture risk in many patients and potentially increase the appearance of undocumented fragility fractures. Correcting PHPT is the first step towards improving long-term bone health. These skeletal issues must be diagnosed and treated both during the workup for PHPT and after its correction. Appropriate Endocrinology referral is needed for long-term medical management for anyone with low bone mass, osteoporosis, undiagnosed fragility fracture, or even significant historical risk factors for early bone loss. Finding a fragility fracture or osteoporosis in the workup for PHPT shows that already years of fracture risk have passed and improving the skeletal risks will take years following their diagnosis. By following the new guidelines in which evaluating bone density, bone loss risks, and fracture are recommended, clinicians can improve the long-term outcomes from osteoporosis and decrease its morbidity and mortality.

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Parathyroid Pathology

30

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Contents

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Introduction

The cytohistologic evaluation of the parathyroid is predicated on understanding the range of normal variation, the underlying pathophysiologic processes that manifest as cytohistologic abnormalities and the utility of pathologic evaluation in guiding surgical and clinical intervention. This chapter focuses on normal variations in the histology of the parathyroid, the cytohistologic changes associated with disease states, diagnostic pitfalls, and the role of cytology and intraoperative frozen section in the evaluation of parathyroid lesions.

The Normal Parathyroid

The parathyroid glands are the endocrine glands which act in conjunction with the parafollicular cells of the thyroid to maintain calcium and phosphate homeostasis. The parathyroid glands directly sense serum free calcium levels via membrane-bound calcium sensing receptors (CaSR) and inhibit parathyroid hormone (PTH) secretion in response to high serum free calcium levels [1]. PTH acts on receptors in the bone to activate osteoclasts, and in the kidneys to synthesize calcitrol, the active form of vitamin D, as well as to stimulate renal tubule calcium absorption and phosphate secretion [2]. Phosphate levels

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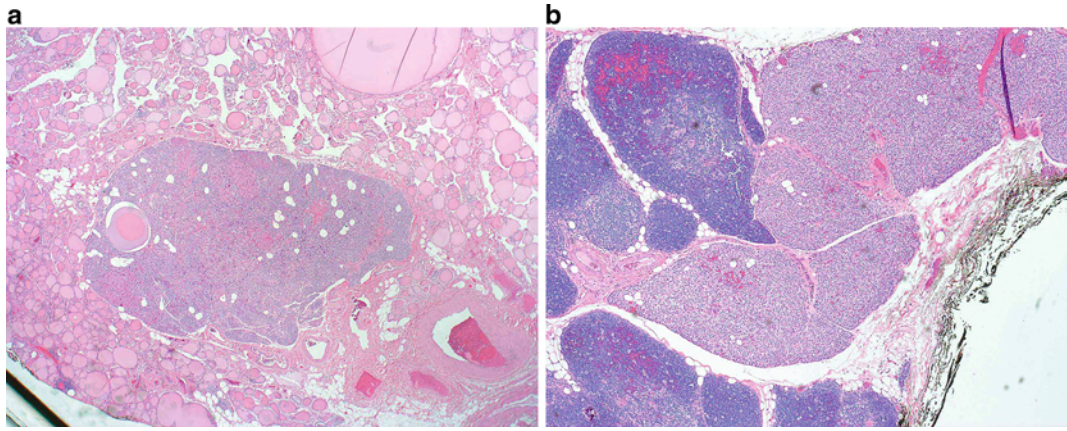

Fig. 30.1 Common ectopic locations for parathyroid glands. (**a**) Intrathyroidal; (**b**) Intrathymic

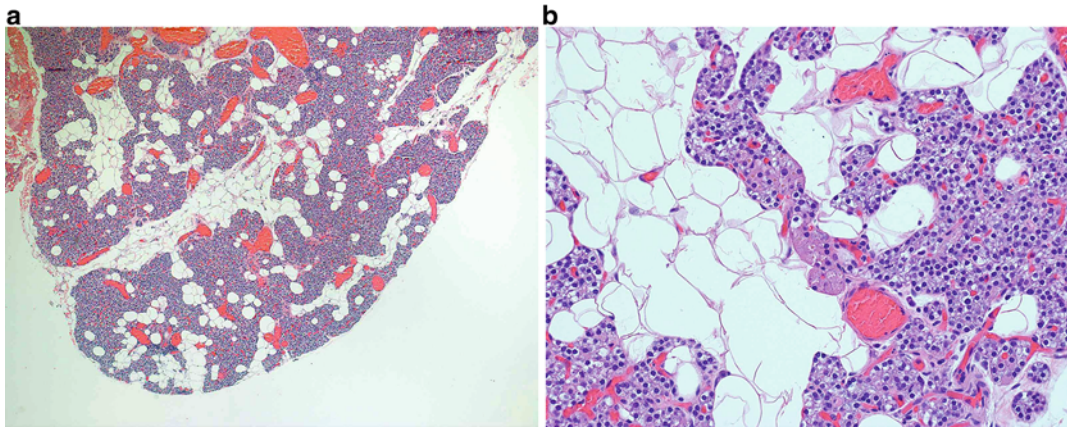

Fig. 30.2 Normal parathyroid. (**a**) Low-power view of a normal parathyroid gland showing a circumscribed but unencapsulated gland composed of nests and cords of parathyroid parenchyma and intervening stromal fat; (**b**) High-power view of normal parathyroid. Predominantly chief cells but also oxyphilic cells and transitional oxyphilic cells can be seen as well as a rich network of parenchymal capillaries and small vessels

indirectly affect parathyroid hormone secretion by binding calcium and thereby reducing the serum free calcium concentration. Elevated levels of calcitrol are sensed by the membrane bound vitamin D receptor (VDR) in the parathyroids and result in downregulation of PTH mRNA transcription [3, 4]. There are typically four parathyroid glands which generally reside immediately posterior to the mid portion and lower poles of the thyroid. However, the presence of supernumerary glands or the absence of one or more glands is not uncommon [5]. The location of the parathyroid glands, particularly the lower parathyroid glands, can vary dramatically as a result of aberrant migration during development and can be anywhere from the central neck to the anterior mediastinum, including within other organs such as the thyroid, larynx, thymus, salivary glands, carotid sheath, lymph nodes, and even pericardium [5, 6] (Fig. 30.1).

The typical parathyroid gland is a thinly encapsulated ovoid gland measuring roughly 6 mm in greatest dimension, weighing roughly 30 mg and composed of chief cells, oxyphilic cells, transitional oxyphilic cells, clear cells, and stromal fat cells (Fig. 30.2). The chief cells are the primary functional unit of the parathyroid and the cell type from which all other parenchymal

cell types are believed to be derived. They are small cells with moderate amounts of slightly eosinophilic to clear cytoplasm containing lipid droplets. They have small hyperchromatic nuclei with neuroendocrine type chromatin. They are typically arranged in nests and cords but may form pseudo-follicular structures which may have an amorphous eosinophilic material. The oxyphilic cells are the true oncocytes of the parathyroid gland and are functionally inactive cells with abundant densely granular eosinophilic cytoplasm filled with mitochondria and small dark nuclei. They are typically absent in children; begin to appear at puberty as single cells and small nests; and increase in number with age. Transitional oxyphilic cells are thought to be cells in transition from chief cell to oxyphilic cells and thus appear in conjunction with oxyphilic cells. Clear cells are a variant of chief cells which derive their appearance from abundant cytoplasmic glycogen. In the setting of normal parathyroids, they are seen primarily in embryos and fetuses and decline dramatically with age. The parenchymal cells of the parathyroid are supported by a rich bed of capillaries supplied by the superior and inferior thyroid arteries [5, 7–9].

The amount of stromal fat within a normal parathyroid is quite variable and is dependent on many factors. The normal parathyroid is composed almost entirely of chief cells until puberty at which point stromal fat appears and gradually increases to about 40–50 % of the total parathyroid mass. Women in general have more stromal fat and therefore slightly larger parathyroids than men. Percentage total body fat is also correlated with the parathyroid stromal fat content and may account for the gender differences. General health and hereditary factors such as race have also been suggested to affect stromal fat content [9]. Since there is significant variability in the "normal" amount of stromal fat within the parathyroid, "hypercellularity" is somewhat difficult to define. However, in adults, marked hypercellularity (>90 %) or the complete absence of stromal fat within a nodule is a good predictor of parenchymal proliferation.

Non-neoplastic Lesions of Parathyroid

Inflammatory Processes

Mild chronic inflammatory infiltrates are not uncommon in the parathyroid and are seen in 10–17 % of patients at autopsy. These infiltrates, tend to be sparse, perivascular, predominantly lymphocytic, and do not appear to be associated with parathyroid dysfunction. Given their association with conditions that affect small vessel integrity such as septicemia, septic shock, and myocardial infarction, these inflammatory infiltrates are speculated to be nonspecific in nature [10, 11].

In contrast, true chronic parathyroiditis is a very rare (<0.1 %) inflammatory process of the parathyroid which presents with diffuse parenchymal involvement, germinal center formation, and evidence of immune-mediated parenchymal reaction, either destructive, in the form of fibrosis and atrophy or alternatively proliferative, in the form of hyperplasia [10] (Fig. 30.3). This apparently paradoxical reaction to the inflammation may be dependent on the nature of the auto antibodies involved, whether cytotoxic or stimulatory, analogous to the findings in the much more common Hashimoto's thyroiditis and Grave's disease of the thyroid [12, 13]. This putative autoimmune etiology is further supported by the identification of autoantibodies to the parathyroid in a subset of patients with this disease and its association with other autoimmune diseases [9, 12]. Treatment is dependent on clinical presentation.

Granulomatous parathyroiditis is a very rare finding usually associated with sarcoidosis and tuberculosis [10, 14]. It typically presents with hyperparathyroidism and in the company of a parathyroid adenoma or hyperplasia but the association is likely coincidental since the vast majority of parathyroidectomies are performed for hyperparathyroidism as a result of parathyroid parenchymal proliferation. The histologic findings are typical of granulomatous inflammation regardless of site and consist of the pres-

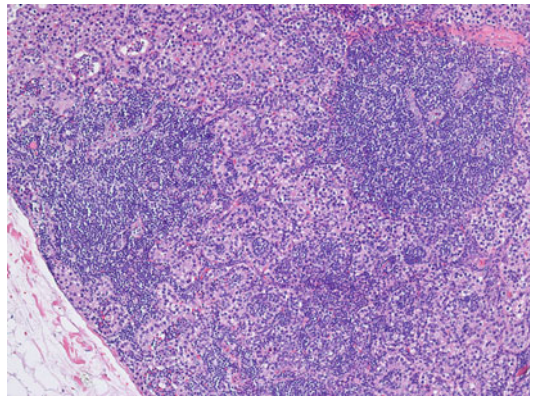

Fig. 30.3 Chronic parathyroiditis. Chronic parathyroiditis in association with parathyroid hyperplasia

ence of giant cells and granulomata with or without central necrosis. The presence or absence of necrosis may be helpful in establishing etiology.

Parathyroid Cyst

Parathyroid cysts are benign cysts of the parathyroid, and are thought to be of developmental or degenerative origin. They may account for up to 5 % of cystic lesions of the neck. They are usually uni-locular with a well-defined capsule and a smooth internal surface. They are variable in size and are usually filled with a clear fluid but may be bloody. Microscopically, they are lined by either chief cells or an attenuated flattened epithelium and may show adjacent normal or hyperplastic parathyroid tissue [15] (Fig. 30.4). Rarely, they are associated with heterotopic tissues such as salivary gland which supports the argument that they may be developmental in nature [16]. While they may be mistaken for thyroid cysts, the distinction is usually clinical insignificant. Since they can occur anywhere a parathyroid can exist, the differential includes other cysts of the neck and mediastinum, depending on site. If clinically relevant, testing the fluid for parathyroid hormone (PTH) may be helpful [15]. Excision is curative.

Parathyroid Parenchymal Proliferations

Parathyroid parenchymal proliferations are classically subdivided into hyperplasias, adenomas, atypical adenomas, and carcinomas. While these categories are conceptually distinct and molecular profiling suggests that they represent discrete entities rather than a spectrum [17–19], there is significant overlap in clinical presentation, gross appearance, histologic features, and immunophenotype. Despite this overlap, there is clinical value to assigning lesions into these discrete categories to stratify risk. We will discuss the classic conceptual categories and their typical histopathologic features and suggest practical considerations for assigning borderline lesions.

Parathyroid Hyperplasia

Conceptually, parathyroid hyperplasias are expansions of the parenchymal mass of the parathyroid in response to stimuli, either internal (i.e. MEN syndromes) or external (i.e. low serum-free calcium). The expansions may be diffuse or multifocal but they involve all of the parathyroid glands to varying degrees. As such, in parathyroid

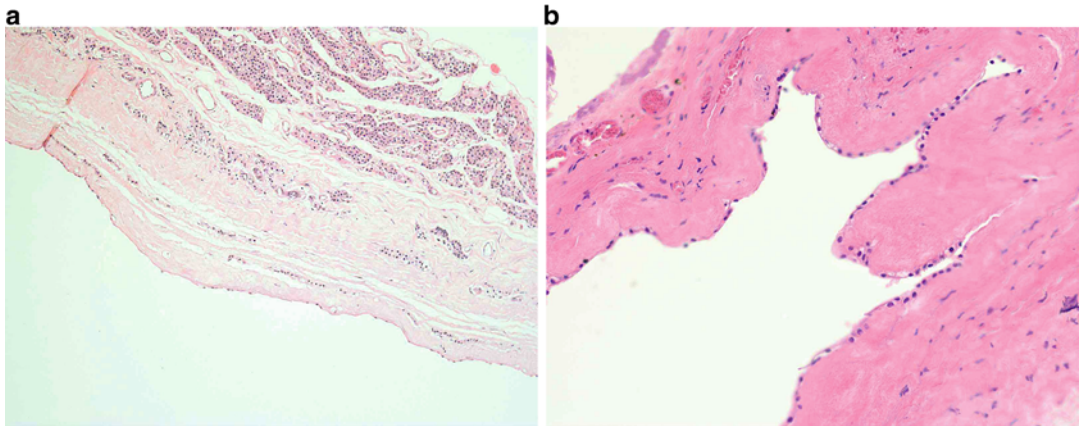

Fig. 30.4 Parathyroid cyst. (**a**) Parathyroid cyst with attenuated lining and adjacent parathyroid tissue; (**b**) High-power view of a parathyroid cyst whose lining is composed of recognizable chief cells

hyperplasia, there is no "normal" parathyroid. This understanding has been recently complicated by evidence that nodular expansions in hyperplasia are clonal in nature whereas diffuse expansions are polyclonal [20–22]. This finding blurs the distinction between hyperplasias, originally thought to be polyclonal in nature, and adenomas which are by definition monoclonal lesions. However, in any proliferating polyclonal population, individual cells are likely to have different proliferative potentials due to accumulated mutations and over time, nodular monoclonal populations arising from individual hyper-proliferative cells are arguably inevitable, with each nodule in a multi-nodular hyperplasia representing an independent clone.

Parathyroid hyperplasia may be primary, secondary, or tertiary depending on the mechanism of pathogenesis. In primary parathyroid hyperplasia, there is an increase in the functional cell mass of the parathyroid in the absence of a known stimulus (i.e. low serum calcium). While generally sporadic, 20–30 % of primary parathyroid hyperplasias are associated with familial hyperparathyroidism syndromes and multiple endocrine neoplasia (MEN) syndromes. In particular, in MEN 1 and MEN2A, 90 % and 30–40 % of patients exhibit parathyroid hyperplasia respectively [8, 9]. Secondary parathyroid hyperplasia is a physiologic response to chronic hypocalcemia, most commonly as a result of chronic renal failure, vitamin D abnormalities, or pseudohypoparathyroidism (end organ resistance to parathyroid hormone). Tertiary parathyroid hyperplasia is a failure to return to a euparathyroid state after the clinical stimulus for secondary hyperparathyroidism, e.g. chronic renal failure, is removed [9]. The mechanism for tertiary hyperparathyroidism is uncertain but there is evidence for both an elevation of the "set point" (concentration of half maximum PTH secretion) and a failure of the hyperplastic parathyroids to involute after removal of the stimulus for hyperplasia [23–26].

Regardless of the mechanism of hyperplasia, the gross and histologic features of parathyroid hyperplasia are similar with only minor differences. In general, the parenchymal expansion may be diffuse or nodular (Fig. 30.5) and range from symmetric to markedly asymmetric in both extent and composition across the parathyroid glands (Fig. 30.6). Total parathyroid gland mass can vary widely but is typically between 1 and 3 g [5]. Generally, all four glands are involved to some extent, in contrast to adenomas, which usually involve a single gland. The expansion of the parenchymal mass is usually predominantly composed of chief cells although there may be expansion of other cell types most commonly oxyphils, and pure expansions of other cell types do rarely occur (Fig. 30.7). This expansion of the parenchymal mass, whether nodular, diffuse or mixed, typically involves the entire gland without a discrete rim of residual normal parathyroid; the distinction between normal and hyperplastic

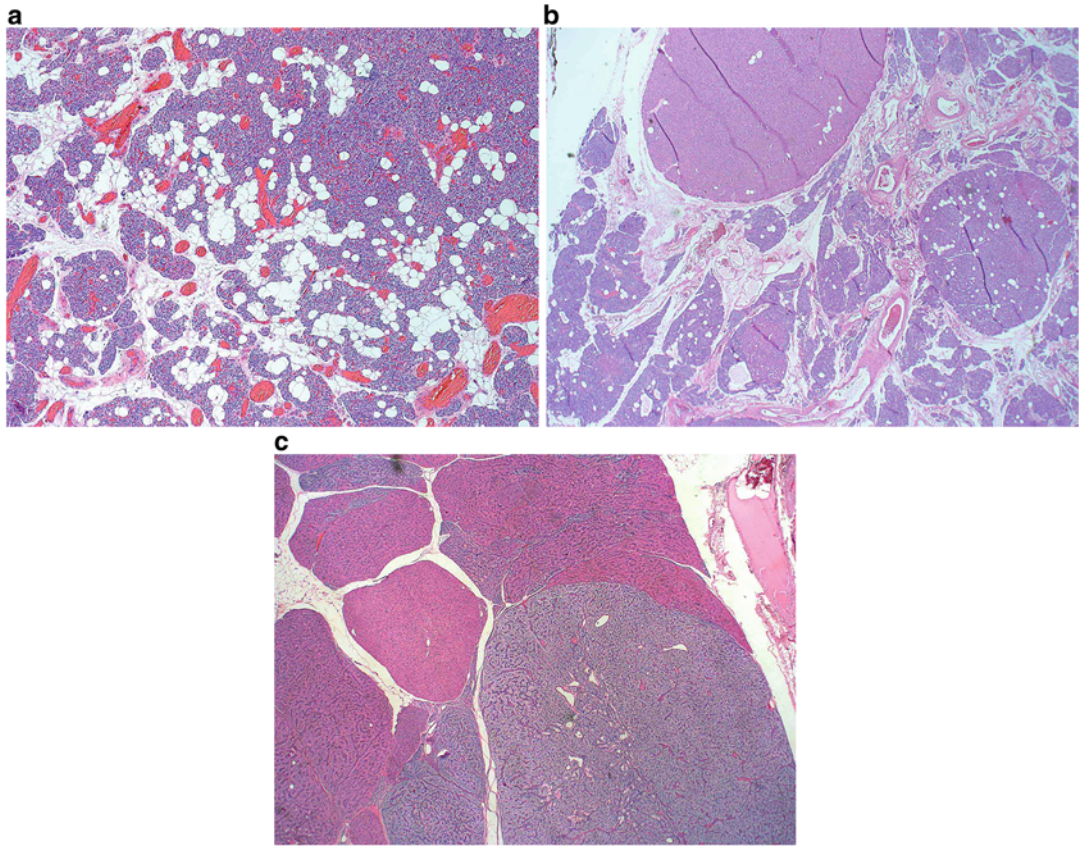

Fig. 30.5 Low-power architectural patterns of parathyroid proliferations. (**a**) Diffuse; (**b**) Diffuse and nodular; (**c**) Nodular

tissue may be histologically difficult. The parenchymal cells can be arranged in diverse architectural patterns including solid sheets, cords, acini, and follicles [5, 9] (Fig. 30.8). As with all neuroendocrine lesions, random nuclear atypia may be present and is not a feature of malignancy (Fig. 30.9). However, uniform atypia is not a feature of hyperplasia and should raise the concern for malignancy. Mitotic activity may be present but is generally low (<1 per 10hpf). Atypical mitoses are not seen. Cystic changes, fibrosis, and calcification are uncommon but increase in prevalence with size and duration of the hyperplasia [9]. Hemorrhagic changes may be present, particularly in tertiary hyperplasias, likely due to the extended duration of the hyperplastic process. These changes are most likely degenerative in nature (Figs. 30.10).

Stromal fat is generally absent within nodular proliferations and decreased in the intervening areas of diffuse proliferation. However, given the inherent variability in the normal stromal fat content and distribution across individuals, hypercellularity is a somewhat tenuous indicator of hyperplasia and is most reliable when marked hypercellularity for age is present. Loss of intracellular fat is common and potentially a more reliable indicator of hyperplasia but some parathyroid hyperplasias can have abundant intracytoplasmic fat and interpretation can occasionally be challenging [9].

Although typically well circumscribed by the parathyroid capsule, hyperplasias, particularly those associated with genetic syndromes, may exhibit small nests of parathyroid tissue outside the capsule ("parathyromatosis") [9, 27]. These

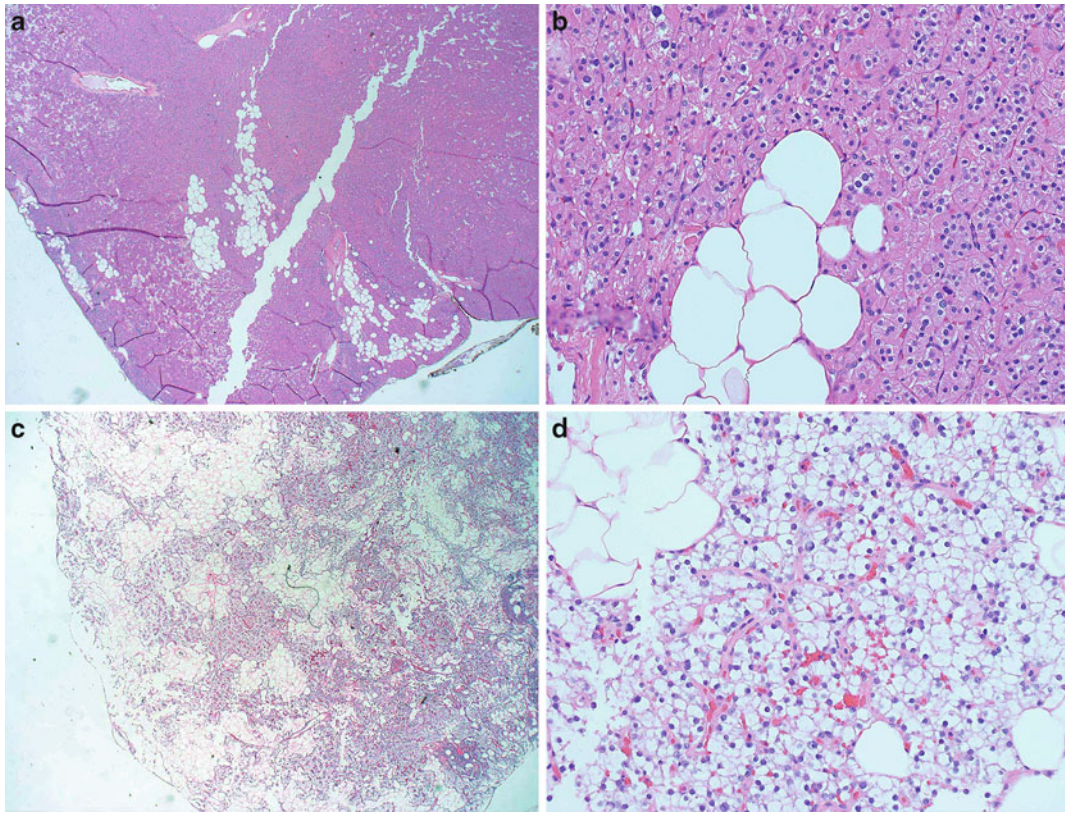

Fig. 30.6 Asymetric size and composition of hyperplastic parathyroid glands. (a, b) Right superior parathyroid with marked hypercellularity and oxyphlic cell predominance 2.1 × 2.0 × 1.5 cm; (c, d) Right inferior parathyroid with normal cellularity and water-clear cell predominance 1.1 × 0.7 × 0.3 cm. Both parathyroids are markedly enlarged. The remaining two parathyroids were of grossly normal size and not sampled

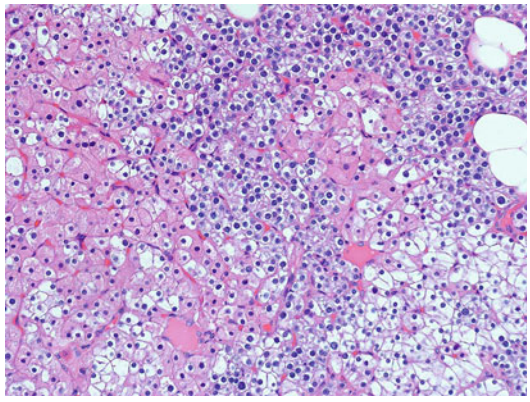

Fig. 30.7 Major parenchyma cell types of parathyroid proliferations: chief cell, oxyphilic cell, and water-clear cell

nests may be primary as in MEN1 or secondary to prior neck surgery. In the latter case, the parathyromatosis is speculated to arise from autoimplantation of cells spilled during the excision of a hyperplastic or neoplastic parathyroid lesion or inadvertent transection of a normal parathyroid [28, 29]. In primary parathyromatosis, these nests can be distinguished from soft tissue invasion by their rounded contours and lack of a desmoplastic reaction. The situation is complicated in secondary parathyromatosis because the reactive fibrosis associated with prior surgery may mimic desmoplasia and produce angulated contours [9, 28]. However, given the relative rarity of parathyroid carcinoma, other criteria should be

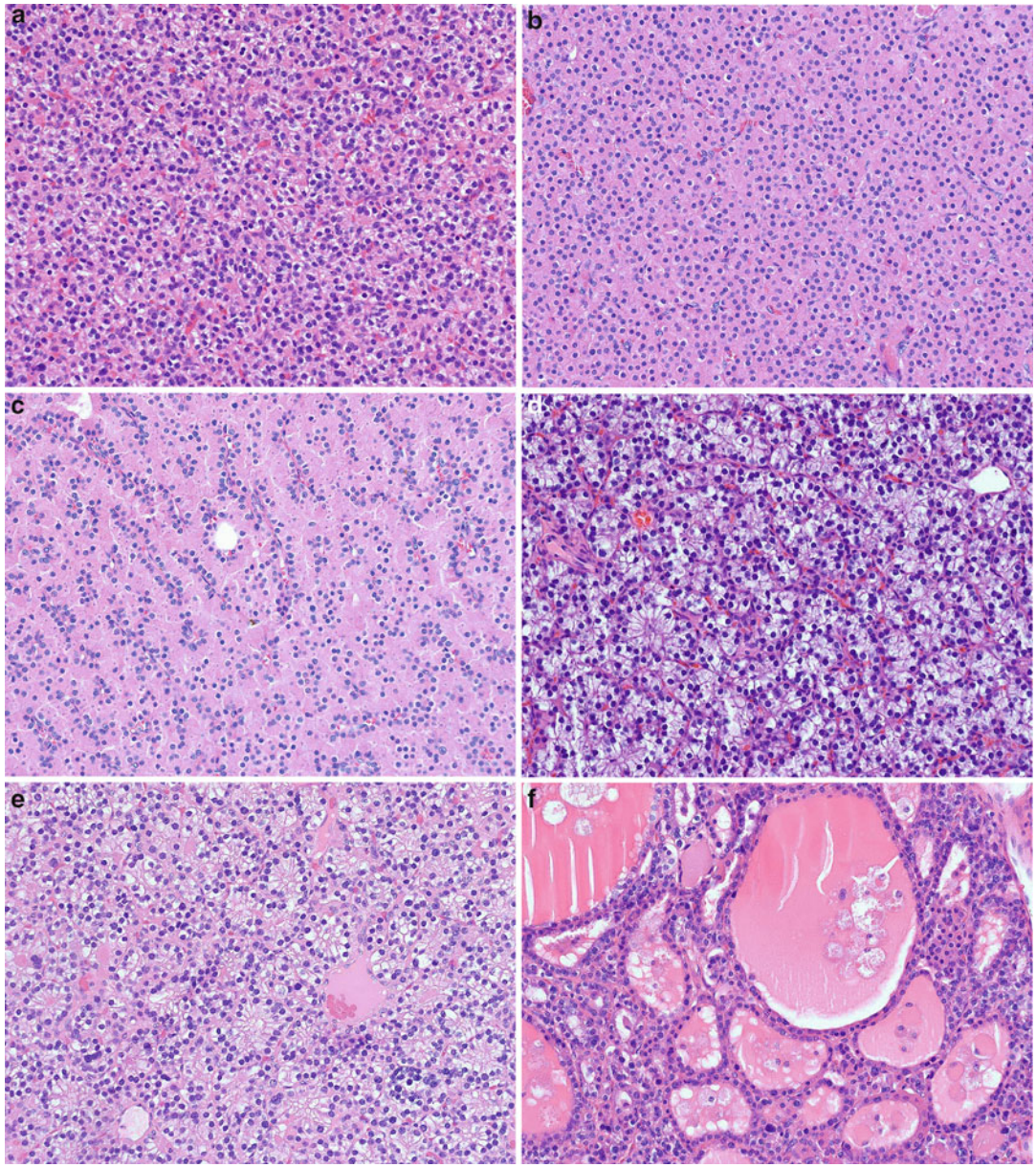

Fig. 30.8 High-power architectural patterns of parathyroid proliferations. (**a**, **b**) Solid; (**c**, **d**) Cords; (**e**) Acinar; (**f**) Follicular

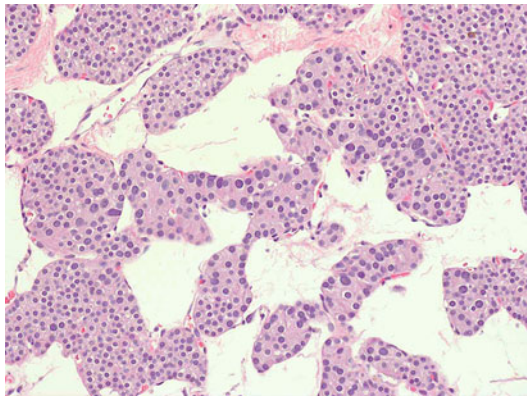

Fig. 30.9 Random nuclear atypia. Note that most of the nuclei are small in regular with only scattered enlarged nuclei

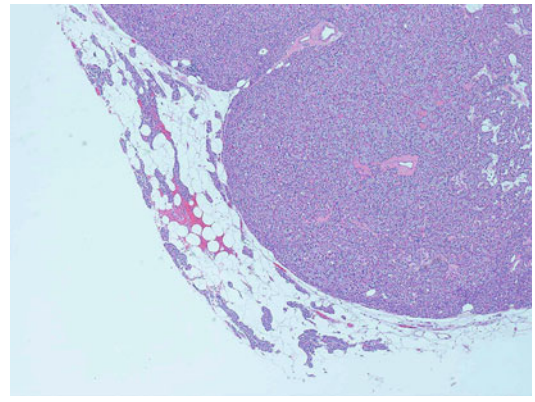

Fig. 30.11 Rim of normal parathyroid tissue associated with parathyroid adenomas

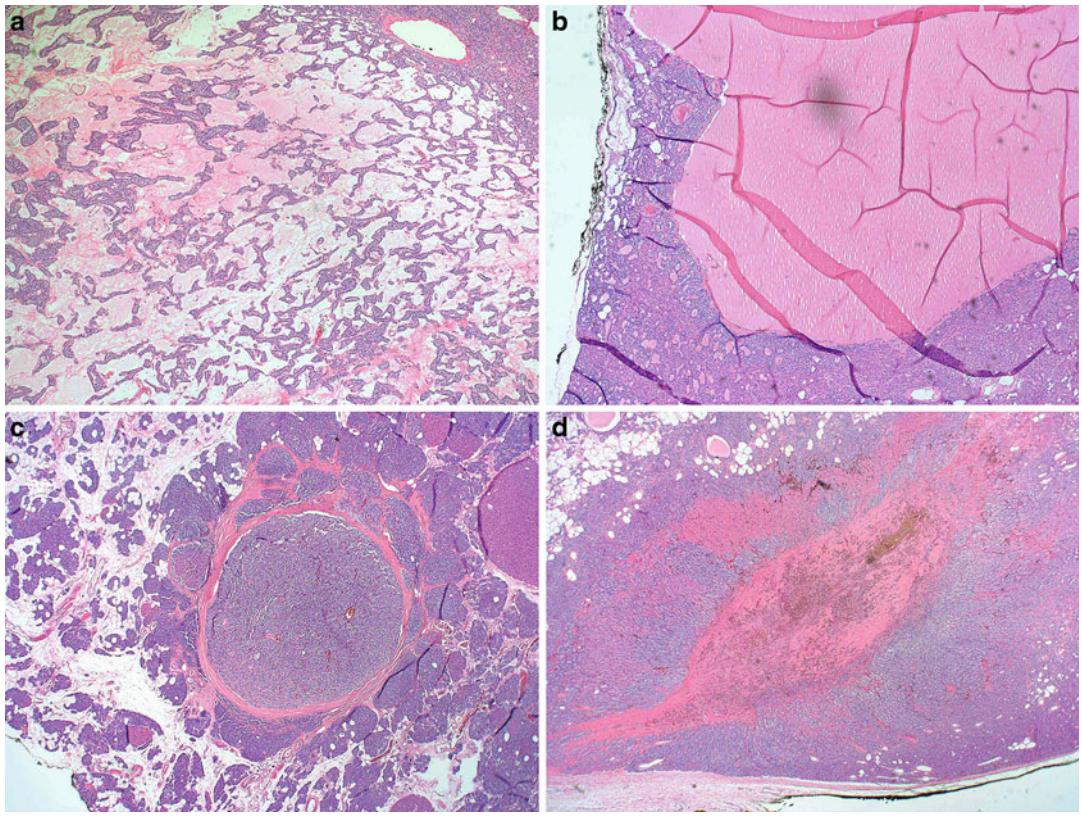

Fig. 30.10 Reactive/degenerative changes in parathyroid proliferations. (**a**) Myxoid degeneration; (**b**) Cyst formation; (**c**) Fibrosis; (**d**) Hemorrhage

applied in the face of prior surgery. In either case, care should be taken to exclude lymphovascular invasion which may have a similar morphology.

Water-Clear Cell Hyperplasia

Water-clear cell hyperplasia is defined by the proliferation of large cells with abundant clear cytoplasm in multiple parathyroid glands. It is a very rare cause of primary hyperparathyroidism and presents with more severe clinical symptoms although it is unclear if this is inherent to the lesion or a byproduct of it's generally larger size (47 % of patients have a mean total parathyroid weight >10 g). It is the only type of hyperplasia which frequently shows greater involvement of the upper glands than the lower ones [5]. The etiology of water-clear cell hyperplasia is unknown although it has been speculated that is may represent a variant of longstanding chief cell hyperplasia. Histologically, the parathyroids are replaced by a proliferation of large clear cells with sharp cytoplasmic borders. These cells may be arranged in cords, sheets, or acini with little or no intervening stromal fat. Periodic acid Schiff (PAS) stain with diastase is positive for glycogen and neutral fat stains are negative for intra-cytoplasmic fat [5, 9]. The overall presentation is distinctive and the main histologic differential diagnosis is metastatic renal cell carcinoma, although clear cell lesions of the thyroid including medullary carcinoma are possible considerations.

Parathyroid Adenoma

Conceptually, parathyroid adenomas are benign autonomous monoclonal proliferations of the parathyroid parenchyma. As such they arise in a background of normal parathyroid tissue and are associated with genetic alternations which release them from the normal physiologic control of proliferation. Two genes have been identified which are associated with this uncoupling, the oncogene cyclin D1 (CCND1)/PRAD1 and the tumor suppressor MEN1 [30]. In the case of cyclin D, an inversion has been identified in up to 8 % of parathyroid adenomas which places the cyclin D1 gene adjacent to the 5′ regulatory elements of the parathyroid hormone (PTH) gene resulting in tissue specific upregulation of cyclin D1 expression. Additionally 30–40 % of sporadic parathyroid adenomas overexpress cyclin D1. In the case of MEN1, inactivating mutations have been identified in up to 30 % of sporadic parathyroid adenomas and the gene itself is implicated in the MEN1 syndromes which are strongly associated with parathyroid proliferations [3, 31].

Grossly, parathyroid adenomas tend to be soft, solitary, circumscribed, and tan to red brown in color. They are typically ovoid but may be lobulated and can range greatly in size from as little as 150 mg to greater than 100 g; most fall between 300 mg and 1 g. They may exhibit degenerative changes such as cyst formation, fibrosis, calcification, and hemorrhage. These changes are more common in larger adenomas [5, 8, 9, 32].

Histologically, parathyroid adenomas are markedly hypercellular and composed predominantly of chief cells although oxyphils, transitional oxyphils, and rarely clear cells may be present and occasionally predominate. These parenchymal cells are usually arranged in sheets and cords, although acinar and follicular architectures may be present and are sometimes prominent. These follicles may contain amorphous eosinophilic material reminiscent of colloid. The neoplastic cells are slightly larger than their normal counterpart but this difference is difficult to appreciate without side by side comparison. Stromal fat is typically absent except in the lipoadenoma variant. The lesion is circumscribed and may be thinly encapsulated. A rim of normal or atrophic parathyroid tissue is present in only 60–70 % of cases but when present is a helpful diagnostic discriminator between adenoma and hyperplasia (Fig. 30.11). Random nuclear atypia involving scattered cells and rare giant cells may be present but uniform atypia should not be seen. Mitotic figures are uncommon but when present generally number less than 1/10 hpf although higher mitotic rate are sometimes seen. Atypical mitoses are not seen [5, 8, 9, 32].

Immunohistochemical studies are not usually necessary for diagnosis but on occasion, the differential includes thyroid neoplasms and clear cell neoplasms from other sites. As with all benign

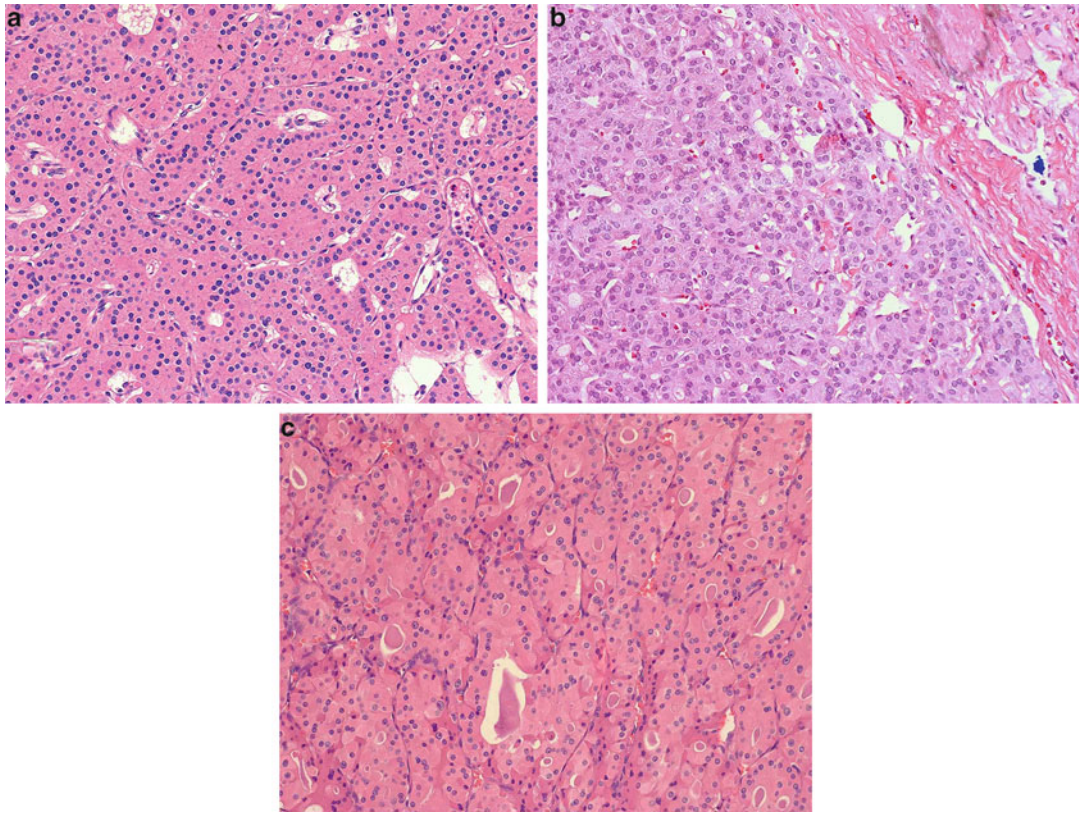

Fig. 30.12 Comparison between oxyphilic variant of parathyroid adenoma and oncocytic thyroid neoplasms. (**a**) Oxyphilic variant of parathyroid adenoma—note the densely granular eosinophilic cytoplasm and hyperchromatic coarsely granular nuclei; (**b**) Oncocytic follicular adenoma—note the less granular cytoplasm and lighter nuclei; (**c**) Hurthle cell adenoma—note the prominent nucleoli, densely granular cytoplasm, sharp cytoplasmic borders

proliferations of the parathyroid, parathyroid adenomas are positive for PTH, parafibromin, chromogranin A, cytokeratin 8/18, Gata-3, Bcl-2, RCC, Pax-8, and mdm2. Pertinent negative stains include TTF-1, thyroglobulin, Pax-2, and CD10. [9, 33–39]. Ki-67 typically shows a proliferative fraction of <5 % [37, 40]. Since a subset of parathyroid adenomas express calcitonin [41], if medullary carcinoma is in the differential, concomitant staining for TTF-1 is recommended as medullary carcinoma is positive for TTF-1 whereas parathyroid adenomas are not.

Histologic Variants

Histologic variants of the parathyroid adenoma include oxyphilic adenomas, lipoadenomas, and water-clear cell adenomas.

As implied by the name, oxphilic adenomas are composed predominantly of oxyphilic cells (>90 %). While originally thought to be nonfunctional, the majority are associated with hyperparathyroidism [42]. They tend to be larger and, interestingly, are more easily detected by sestamibi scan than their chief cell counterparts [43]. From a diagnostic standpoint, they are significant for their ability to closely mimic oncocytic thyroid neoplasms (Fig. 30.12), a dilemma which is complicated by their proximity to the thyroid, their rare intrathyroidal location, and occasionally, the presence of follicular architecture. This diagnostic dilemma is readily resolved by immunohistochemical studies due to their differential staining for TTF-1(−), thyroglobulin(−), Gata-3(+), and PTH(+). The key to avoiding this pitfall is to be aware that it exists.

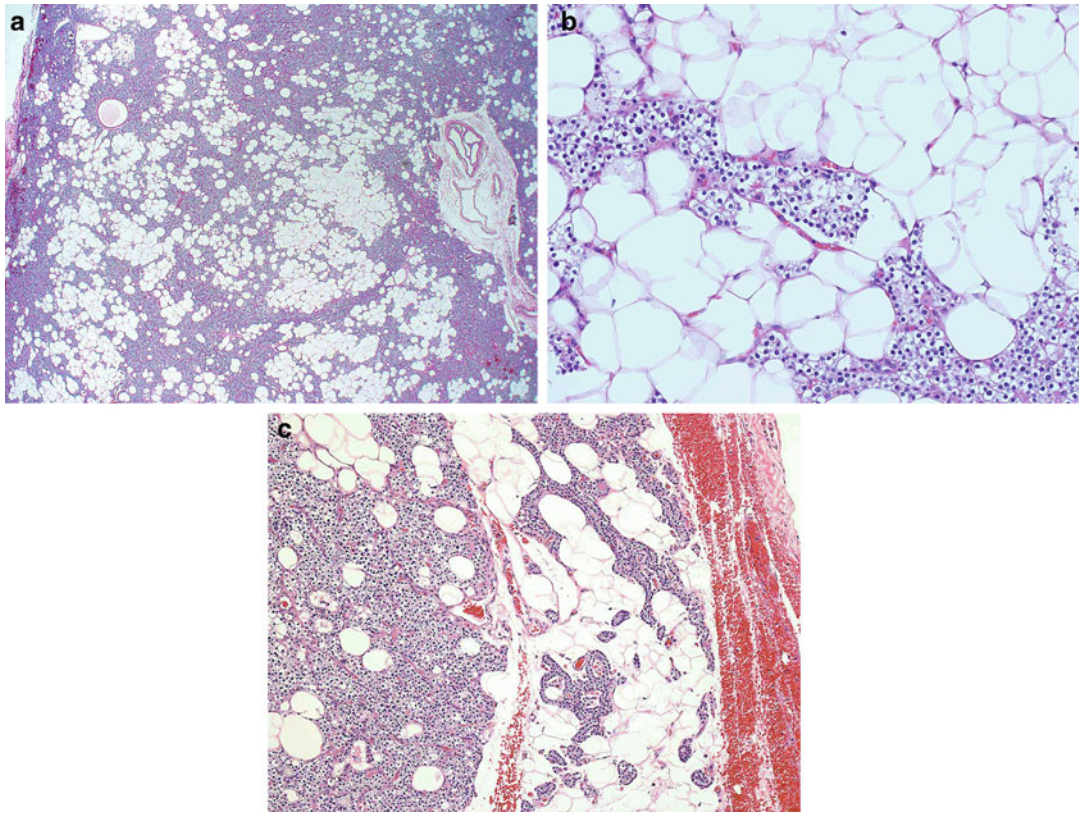

Fig. 30.13 Lipoadenoma. (**a**) Low power showing abundant stromal fat; (**b**) High power; (**c**) Adjacent rim of normal tissue. Note the cells of the adenoma are larger than the adjacent normal tissue

The lipoadenoma is a very rare histologic variant (<50 cases in the literature) showing abundant stromal fat admixed with nests and cords of parathyroid parenchyma (Fig. 30.13). Degenerative myxoid changes and heterologous elements may be present. Whether the lipoadenoma is a true variant of a parathyroid adenoma or a distinct entity is unclear at this time. While most are associated with hyperparathyroidism, the biochemical findings are typically milder than similar size adenomas, likely the result of their relatively lower parathyroid parenchymal mass. They are difficult to localize by sestamibi scan, likely due to their high fat content and may be mistaken for lipoma or normal parathyroid in small biopsies/fine needle aspiration [44]. Histologic diagnosis on excision specimens is usually straightforward due to their size and typical appearance.

The water-clear cell adenomas is an even rarer functional variant of parathyroid adenoma with perhaps a dozen reported cases in the English literature. These adenomas are composed of large clear cells with vacuolated cytoplasm containing abundant glycogen, morphologically identical to those seen in the more common water-clear cell hyperplasias. Unlike water-clear cell hyperplasias, water-clear adenomas usually involve only a single parathyroid gland, although a single case of a water-clear cell double adenoma has been reported [45]. Given their rarity and focality, the main diagnostic consideration is to avoid mistaking these lesions for metastatic clear cell malignancies. This is a significant consideration because water-cell cell adenomas are histologically very similar to metastatic clear cell renal cell carcinomas (Fig. 30.14) which are surprisingly common in and around the thyroid. Many clear

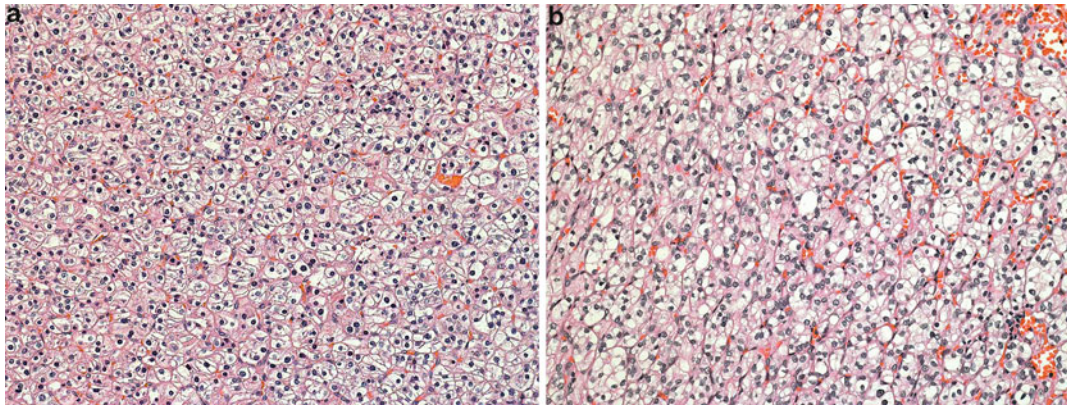

Fig. 30.14 Water-clear cell parathyroid proliferations versus metastatic renal cell carcinoma. (**a**) Water-clear cell adenoma; (**b**) Metastatic renal cell carcinoma. The two lesions are virtually indistinguishable on histology

cell renal cell carcinomas have low cytologic grade which make them difficult to distinguish from benign clear cell lesions. In addition, water-clear cell adenomas stain for both RCC and Pax8, two markers often used to identify metastatic renal cell carcinomas. Furthermore, renal cell carcinomas can often secrete PTH related peptide (PTHrp) resulting in hypercalcemia and thus have similar clinical presentations, although PTH itself is usually suppressed [46]. Fortunately, as long as the existence of this variant is recognized, an appropriate immunohistochemical panel including CD10, Pax2, TTF-1, Gata-3, and PTH can readily distinguish water-clear cell adenomas from metastatic renal cell carcinoma as well as clear cell lesions of other sites.

Double Adenomas

The concept of double and even triple adenomas is controversial [47]. Much of the debate centers not so much on the existence of these lesions but rather, their prevalence. While there is no logical reason to believe that multiple parathyroid adenomas cannot arise independently, given the rarity of parathyroid adenomas in the general population (<1 %) [9], if they are independent events, the incidence of double adenomas should be quite low, and triple adenomas should be reportable. Despite this, the incidence of double adenomas has been reported to be as high as 15 % [48]. Supporters of the higher rate of multiple adenomas typically point to biochemical cure as proof [48, 49]. However, since parathyroid surgeries remove the significant bulk of the parenchymal mass and hyperplasias are typically slow growing lesions, the remaining tissue may simply be insufficient to produce a biochemical abnormality for some time. Certainly, the well documented, if uncommon, recurrence of hyperparathyroidism after parathyroidectomy for an "adenoma" suggests some asymmetric nodular hyperplasias are mistaken for adenomas [50]. This reality is highlighted by the fact that the incidence of "double adenomas" appears to be dependent on the surgical approach (unilateral versus bilateral) [51, 118], yet biochemical cure rates do not appear to be significantly impacted by approach, at least in the short term [52].

It is unclear how much parathyroid tissue is minimally required for a euparathyroid state or how much is needed to produce clinical hyperparathyroidism. The presence of parathyroid incidentalomas in normocalcemic patients [53], and the transient effect of the inadvertent partial parathyroidectomies which occur during thyroid surgery [54–57] suggest that there is a relatively broad range of parathyroid parenchymal mass which will produce a euparathyroid state. Molecular studies suggest that "double adenomas" may arise in the background of hyperplasia [58], which leads to the question of what distinguishes an adenoma from a nodular hyperplasia? While these debates are important, from a practical

standpoint, they may be academic. With the advent of intraoperative monitoring of PTH and goal of surgery to bring intraoperative PTH levels to normal range, sufficient tissue may be removed to make it a moot point whether the remaining tissue is normal or hyperplastic [59]. The major consideration of this debate is arguably long-term follow-up. Given the results of molecular studies which suggest that double adenomas may arise in hyperplasias [58] and long-term follow-up studies that show that both hyperplasia and double adenomas show higher recurrence rates of hyperparathyroidism than single adenomas [50, 52], it may be prudent to follow all patients with double adenomas for an extended period.

Adenoma vs. Hyperplasia: The Example of Lithium Induced Hyperparathyroidism

A prime example of the difficulties in reliably distinguishing between adenoma and hyperplasia is lithium induced hyperparathyroidism. Lithium induced hyperparathyroidism occurs in approximately 10 % of patients taking lithium. The mechanism of lithium induced hyperparathyroidism is unknown but it has been speculated lithium competitively binds to CaSRs, effectively increasing the free calcium set-point as well as increasing renal tubule reabsorption of calcium [60]. Since lithium exposure is systemic and withdrawal of lithium is often curative [61], lithium induced hyperparathyroidism should logically be due to hyperplasia [62, 63] analogous to the case of chronic renal failure. However, when surgeries are performed to treat lithium induced hyperparathyroidism, the bulk of the lesions are called adenomas [62, 64, 65]. While it has been speculated that lithium therapy may unmask subclinical primary hyperparathyroidism, this does not explain the observation that cessation of lithium therapy is often curative. It is much more likely that asymmetric parathyroid hyperplasias are being diagnosed as adenomas. This is supported by the high recurrence rate of lithium induced hyperplasias [64]. Given that nodular proliferations in secondary hyperplasias are clonal, it is not surprising that they would be individually indistinguishable from adenomas. The fact that there is low inter-observer concordance between parathyroid adenoma and hyperplasia does not help the situation [66].

If we accept that we cannot reliably distinguish between adenomas and asymmetric hyperplasias histologically, where does this leave us? While the current management, i.e. minimally invasive parathyroidectomy, appears to be effective in the short term (5 years or less), the higher recurrence rates seen in cases of "double adenoma" and lithium induce hyperparathyroidism suggest that we should treat them as hyperplasias with bilateral exploration and possibly subtotal parathyroidectomy.

Atypical Adenoma

Conceptually, an atypical parathyroid adenoma is a neoplasm which shows some histologic features worrisome for malignancy (Figs. 30.15 and 30.16) but does not have diagnostic malignant features such as infiltrative growth (capsular or soft tissue invasion), lymphovascular invasion, perineural invasion, or metastasis. These worrisome features include a thickened capsule, irregular capsular contours, entrapped intracapsular nests, trabecular growth pattern (Fig. 30.17), internal fibrosis, increased mitotic activity (>1 per HPF but <5 per HPF), atypical mitoses, coagulative necrosis, uniform atypia, and prominent nucleoli [5, 7–9]. Immunohistochemical studies also show a profile which is intermediate between adenoma and carcinoma [35, 37, 38, 67, 68]. Since molecular profiling studies do not support a progression from adenoma to carcinoma [17–19], this category most likely represents a heterogenous mix of adenomas and low-risk carcinomas which have overlapping histologic features rather than a true intermediate entity. Long-term follow-up in patients with atypical adenomas is quite scant but what little data there is suggests that these lesions are indolent with only rare cases of subsequent identification of overt malignancy [68–70]. As such, while patients require more aggressive follow-up for recurrence and

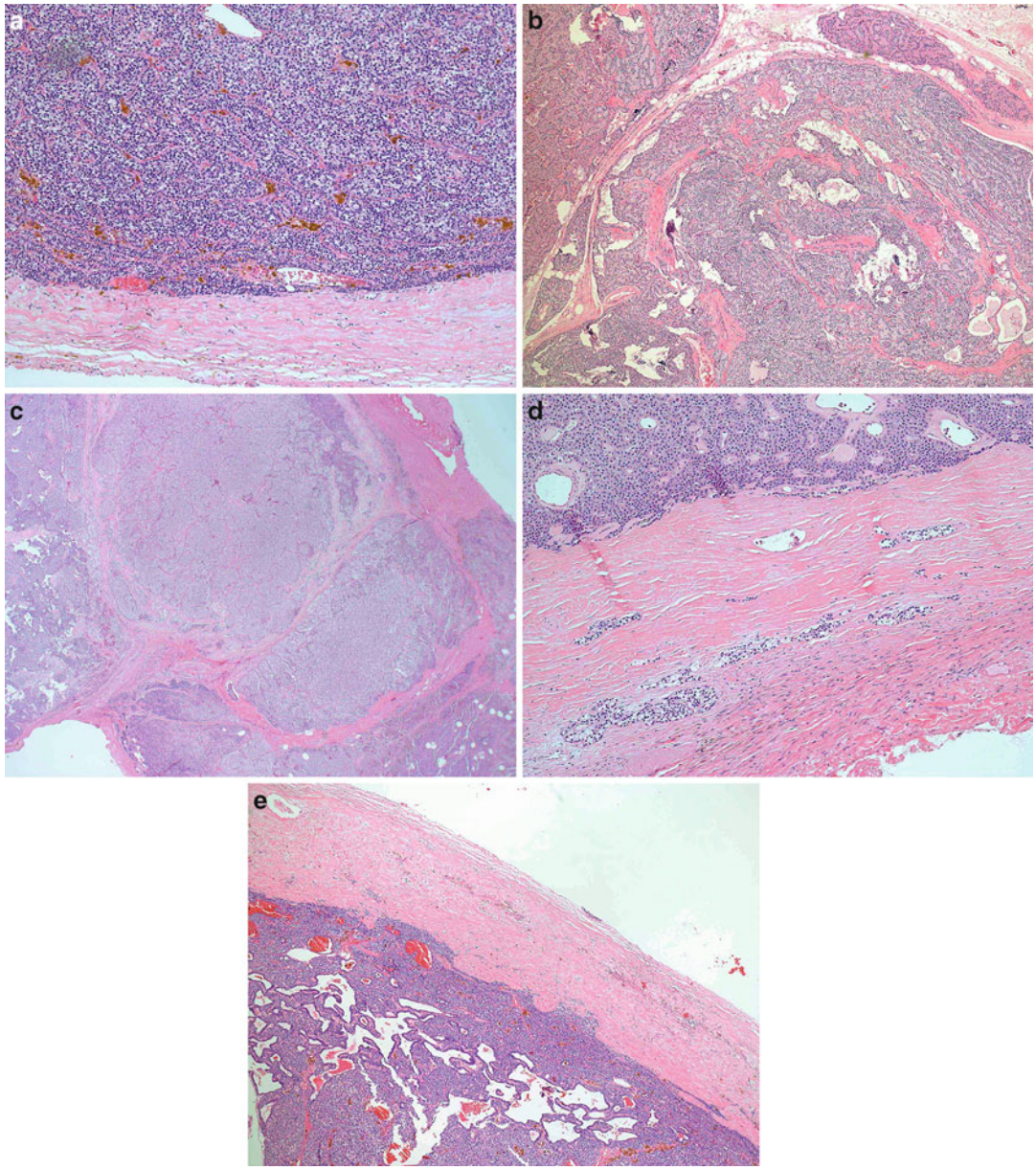

Fig. 30.15 Worrisome low-power features of parathyroid proliferations. (**a**) Thick capsule; (**b**) Internal fibrosis; (**c**) Lobulated architecture; (**d**) Intracapsular nests; (**e**) Capsular irregularities

surveillance for metastasis, the clinical course will most likely be benign.

Parathyroid Carcinoma

Conceptually, parathyroid carcinoma is a malignant neoplasm arising from the parenchymal cells of the parathyroid which has both locally invasive and metastatic potential. Parathyroid carcinoma arises de novo rather than as a malignant transformation of existing adenomas [17–19]. It is a very rare malignancy and usually presents with marked hypercalcemia but may be nonfunctional [71]. Aberrant expression of various oncogenes and tumor suppressor genes have

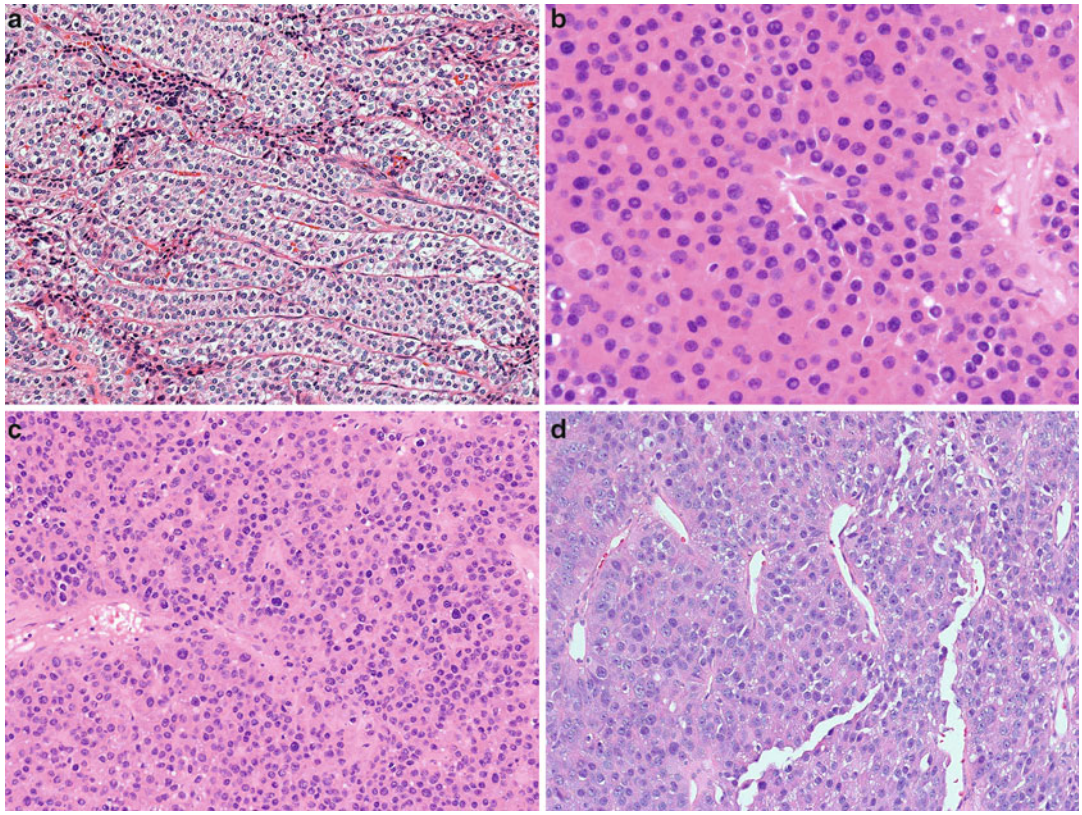

Fig. 30.16 Worrisome high-power features of parathyroid proliferations. (**a**) Trabecular growth pattern; (**b**) Increased mitotic activity; (**c**) Uniform nuclear atypia; (**d**) Prominent nucleoli (also uniform atypia)

been identified in parathyroid carcinoma [72] but the HRPT2 gene is thought to play the primary role in carcinogenesis [35, 38, 73–78].

Grossly, parathyroid carcinomas tend to be somewhat larger than their benign counterparts but there is significant overlap. They typically presents as solitary white, firm, irregular, adherent masses, often described as difficult to dissect from surrounding tissues [5, 8, 9, 79]. This is in contrast to hyperplasias and adenomas which are tan to red brown, soft, well circumscribed, and easily excised.

The histologic diagnosis of parathyroid carcinoma is challenging. Histologic evaluation does not correlate well with clinical behavior [80, 81]. Likely factors producing this inconsistency include the inexperience on the part of the pathologist and surgeon due to the rarity of this disease; it is generally low-grade cytology; the locally aggressive nature of parathyromatosis, whether benign or malignant in nature; diagnostic dilemmas associated with prior fine needle biopsy or previous neck surgery; and the evolution of diagnostic criteria for malignancy [82].

Histologically, parathyroid carcinomas tend to have low cytologic grade and are composed of the same parenchymal cell types as parathyroid adenomas and hyperplasias. The histologic criteria for parathyroid carcinoma were first proposed by Schantz and Castleman [83] and included the presence of a thickened fibrous capsule or fibrous intra-lesional trabeculae; trabecular or rosette-like architecture; mitotic activity and capsular or vascular invasion. Later, additional features were noted including lobular architecture, irregular capsular contours, entrapped intracapsular nests, atypical mitoses, coagulative necrosis, uniform atypia, perineural invasion, and prominent nucle-

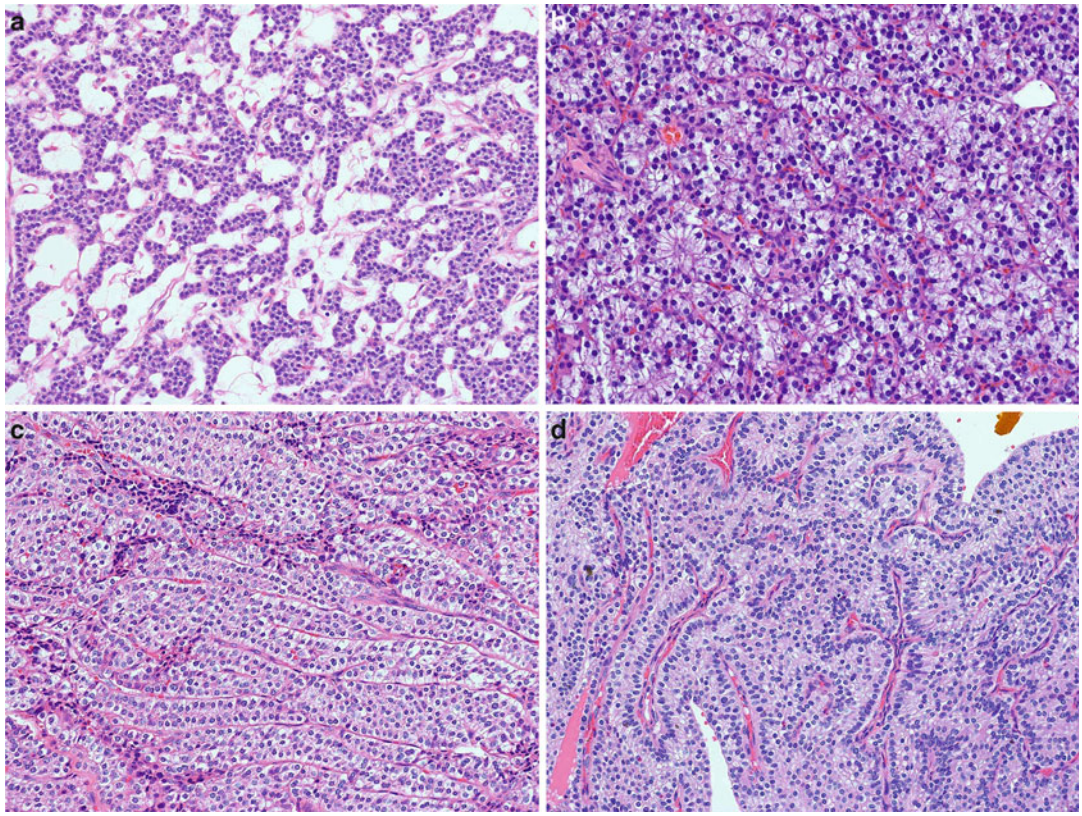

Fig. 30.17 Cords versus trabeculae. (**a**, **b**) Cords; (**c**, **d**) Trabeculae. While both cords and trabeculae form both linear and branching patterns, cords are thinner (1–2 cells thick) while trabeculae are thicker (3+ cells in thickness)

oli [5, 8, 9]. However, many of these features have also been identified in atypical adenomas and rarely, typical adenomas. While all of these characteristics are more common in parathyroid carcinomas and should prompt careful evaluation, the diagnosis of parathyroid carcinoma should rest on unequivocal malignant characteristics such as capsular invasion, lymphovascular invasion, perineural invasion, soft tissue invasion, or distant metastasis [84] (Fig. 30.18).

Because parathyroid carcinoma has proven to be such a difficult histologic diagnosis, significant research has focused on ancillary studies, in particular, the HRPT2 gene. Molecular studies suggest that up to 77 % of aggressive parathyroid carcinomas have mutations in HRPT2 [74, 75]. Unfortunately, 20 % of mutations lie outside mutational hotspots in exons 1, 2 and 7, and would require total gene sequencing to identify. Furthermore, many mutations are large deletions and some cases of HRPT2 downregulation appear to be epigenetic [82], neither of which can be identified by sequencing. These factors make the routine HRPT2 sequencing in parathyroid lesions impractical.

This has led to interest in parafibromin, the protein product of HRPT2. Immunohistochemical (IHC) studies of parafibromin in parathyroid carcinoma have been a mixed bag with some authors showing that loss/reduction of parafibromin nuclear staining is highly sensitive and specific for parathyroid carcinoma [38] while others have had considerably less promising results [82]. These discrepancies can be partially attributed to differences in selection criteria (behavior vs. histology); differences in assay protocols (different primary antibodies and retrieval methods); differences in the criteria for scoring reactivity; and finally, sample size. The results do suggest that loss of parafibromin is a feature of atypical adenomas and carcinomas but not typical adenomas. To improve sensitivity, parafibromin has been

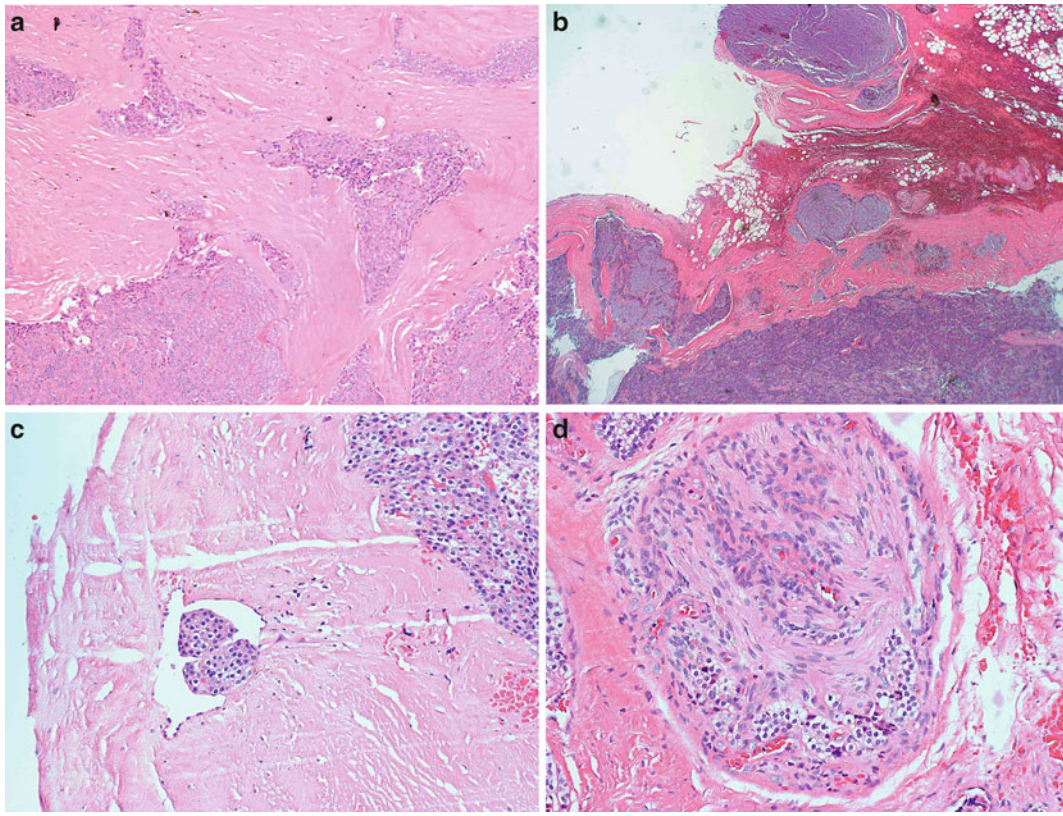

Fig. 30.18 Diagnostic features of malignancy in parathyroid carcinoma. (**a**) Capsular invasion; (**b**) Soft tissue invasion; (**c**) Lymphovascular invasion; (**d**) Perineural invasion

incorporated into IHC panels with other proteins associated with parathyroid carcinoma such as APC, Rb, Galectin-3, PGP9.5, and Ki-67, with promising results [40, 67, 85]. Loss of parafibromin also appears to independently predict recurrence/metastasis [68, 86]. Overall, these findings support the use of parafibromin IHC studies in the evaluation of parathyroid carcinomas and atypical adenomas. Given the technically difficult nature of the assay, testing should be done in a lab with significant experience and consistent results.

No standard staging system exists for parathyroid carcinoma. However, a number of histologic features have been identified as negative prognostic indicators including vascular invasion, lymph node metastasis, invasion into surrounding organs, and distant metastasis [87–89]. Based on these indicators Talat and Schulte [88] have proposed two classification systems, a classic TNM system and a binary high- and low-risk classification system. Both systems appear to be robust on retrospective Kaplan Meyer survival analysis [87, 88]. Immunophenotypic markers have also been correlated with survival/recurrence, including parafibromin, CaSR, and PGP9.5 [68, 86] and may ultimately need to be incorporated into any standard prognostic algorithm.

Other Neoplasms of the Parathyroid

There are rare case reports of paragangliomas [90] and carcinosarcomas [91] of the parathyroid.

Secondary Malignancies of the Parathyroid

Metastatic disease to the parathyroids is uncommon but has been demonstrated in up to 12 % of patients with widespread metastatic disease at autopsy. This rather high percentage represents

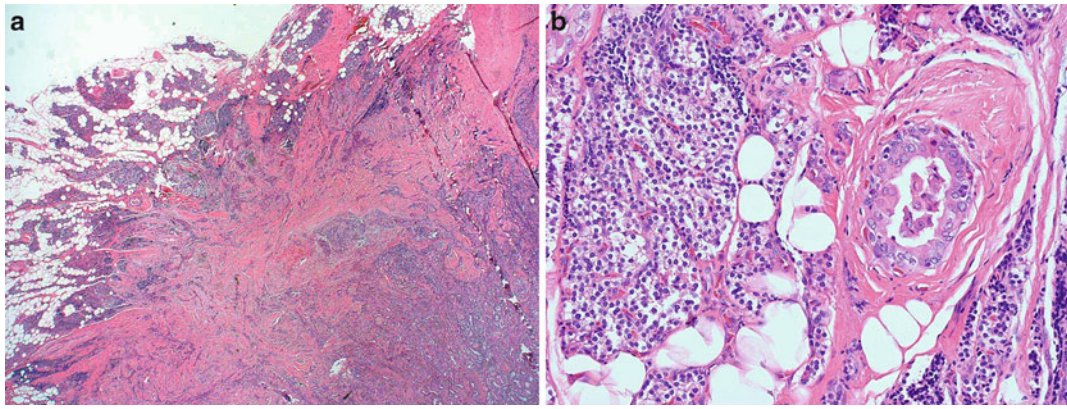

Fig. 30.19 Direct invasion of parathyroid by papillary thyroid carcinoma. (**a**) Low power showing infiltration of parathyroid with desmoplastic reaction; (**b**) High power showing nest of papillary thyroid carcinoma inside parathyroid

an end stage process; metastatic disease to the parathyroid as an initial presenting diagnosis is much rarer (<0.5 % of all parathyroidectomies). The most common primary sites in descending order of prevalence are: breast, melanoma, hematopoietic malignancies, lung, prostate, and kidney [92]. These metastases may present in one or more glands and are not usually associated with hyperparathyroidism. Since most of these metastatic lesions are high grade and present in late stages of the disease, diagnosis of metastatic disease is not usually challenging, although as previously noted, metastatic renal cell carcinoma can be mistaken for water-clear cell adenoma/carcinoma.

Direct extension into the parathyroid from thyroid primaries has also been reported and may be seen in up to 4 % of thyroid carcinomas [92, 93] (Fig. 30.19).

Cytology of the Parathyroid

The purpose of fine needle aspiration (FNA) is to evaluate mass lesions for clinical triage. Parathyroid fine needle aspirations are usually performed either to evaluate a misidentified "thyroid nodule" or to characterize putative parathyroid adenomas identified by ultrasound in patients whose parathyroid adenoma cannot be localized by sestamibi scan. Frequently, the distinction between a posteriorly located thyroid nodule and a parathyroid lesion cannot be made on ultrasound and as a result, parathyroid proliferations are often mistaken for thyroid nodules and aspirated as such. This has become increasingly common as thyroid FNA has become the standard triage modality for thyroid nodules. The distinction between parathyroid proliferations and thyroid neoplasms is challenging on cytology; in fact, most parathyroid proliferations are mistaken for thyroid lesions on FNA, in part due to this misidentification of the biopsy site [94–96]. This situation is further complicated by the rare true intra-thyroidal presentation of parathyroid proliferations [97].

Cytologically, parathyroid adenomas, hyperplasias, and even carcinomas cannot reliably be distinguished because they share low-grade cytology and consist of proliferations of the same parenchymal cell types. Normal parathyroids are generally not biopsied as they are too small to be palpated or visualized by ultrasound. On cytology, parathyroid proliferations usually exhibit marked cellularity composed of a monotonous population of small uniform chief cells arranged in loose three dimensional groups, some with "microfollicular" architecture; flat uniform sheets; and pseudo-papillary structures with fibrovascular cores (Fig. 30.20). Single cells and naked nuclei tend to be abundant. Focal anisokaryosis may be seen, consistent with random nuclear atypia. Chromatin is of the neuroendocrine "salt and pepper" type and rare pseudo-

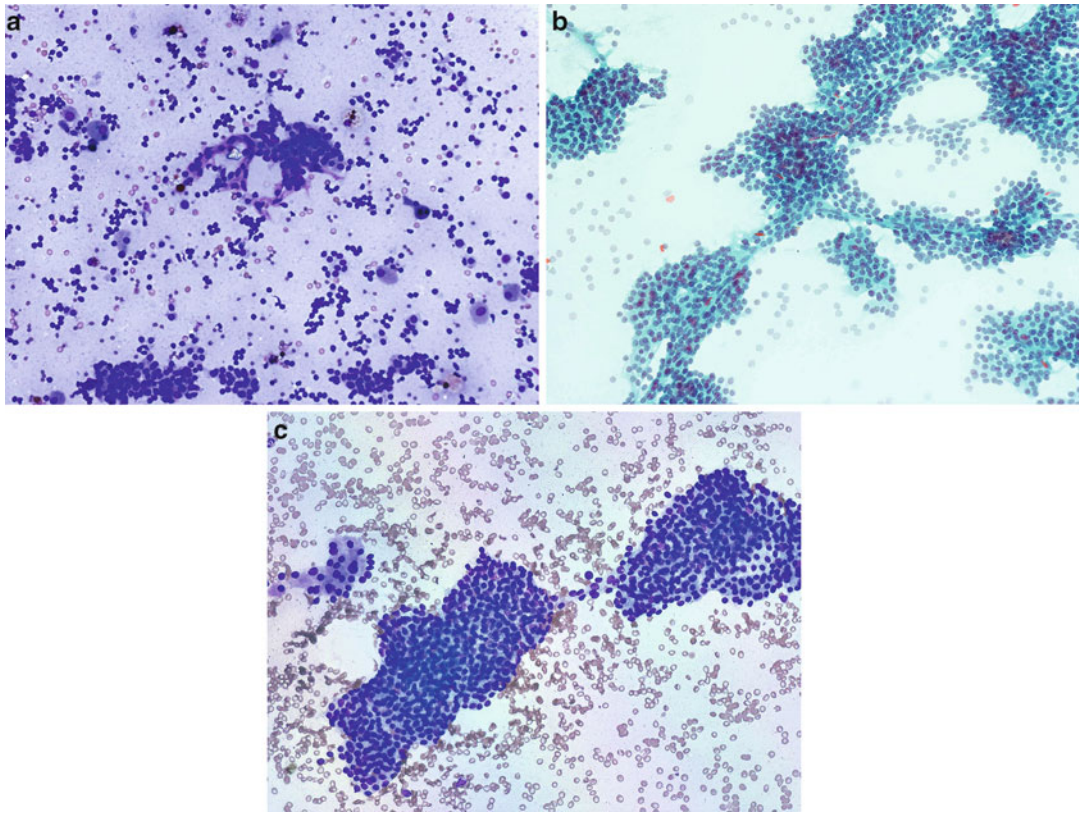

Fig. 30.20 Cytologic features of chief cell predominant parathyroid neoplasms. (**a**) Hypercellular specimen composed predominantly of small, high N/C ratio cells with abundant naked nuclei and three dimensional groups, some with microfollicular and/or pseudopapillary architecture; (**b**) Pseudopapillary architecture is often best appreciated on Pap stain; (**c**) In this context, a dual population with larger oxyphilic cells may be helpful in recognizing a parathyroid proliferation

inclusions may be seen. Thin "colloid" is generally absent (except in partially cystic lesions) but amorphous eosinophilic material resembling thick colloid may be present. Larger oxyphilic cells, with abundant densely granular cytoplasm, often arranged in syncytial clusters, may also be present in variable numbers [94, 95, 98, 99].

This cytologic appearance most closely resembles that of follicular neoplasms, Hashimoto's thyroiditis, and medullary and insular carcinomas. Benign colloid nodules are generally not in the differential because they tend to be hypocellular with abundant colloid. Papillary carcinomas are often hyper-cellular but this cellularity is predominantly composed of larger cells in cohesive sheets with sharply defined cellular borders and true papillary structures with smooth contours. Papillary carcinomas also have characteristic nuclear features such as nuclear clearing, elongation, fine grooves, fine chromatin, and pseudo-inclusions.

In contrast, follicular neoplasms are cellular, monotonous, and have 3-dimensional architecture, all features seen in parathyroid proliferations. Four features which help distinguish follicular neoplasms from parathyroid proliferations are: (a) the relative scarcity of naked nuclei (although excessive pressure during smearing may produce naked nuclei in any specimen); (b) overall greater cohesiveness with few single cells, and (c) a lack of significant pseudopapillary architecture; and (d) larger nuclear and cellular size (Fig. 30.21).

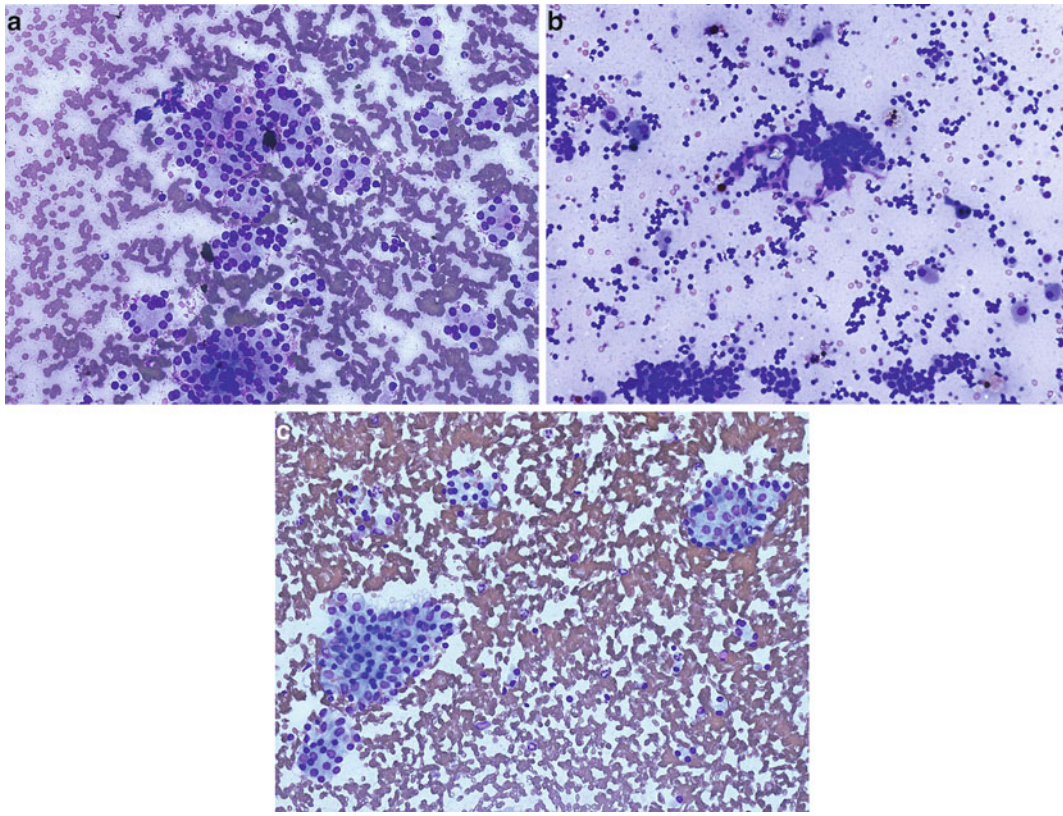

Fig. 30.21 Cytologic comparison of chief cell predominant parathyroid proliferations and follicular neoplasms. (**a**, **c**) Follicular neoplasms; (**b**) Parathyroid adenoma. Note the fewer naked nuclei and single cells and the larger nuclear size and more abundant cytoplasm in the follicular neoplasms. Also pseudopapillary architecture is uncommon in follicular neoplasms

Parathyroid proliferations resemble Hashimoto's thyroiditis because naked nuclei can be mistaken for lymphocytes but in good cytologic preparations, lymphocytes will retain a thin basophilic rim of cytoplasm and typically exhibit crush artifact while naked nuclei do not. In addition, in Hashimoto's thyroiditis, the lymphocytes are much smaller than the nuclei of the follicular cells whereas in parathyroid proliferations, the size of the naked nuclei and those in intact cells is the same. Furthermore, in Hashimoto's thyroiditis, close evaluation identifies lymphocytes within the epithelial groups, which are themselves oncocytic whereas the epithelial groups of parathyroid proliferations are usually not oncocytic.

Medullary and insular carcinomas resemble parathyroid proliferations because they are cytologically bland, hyper-cellular, loosely cohesive malignancies. However, in medullary carcinoma, the cells are larger, naked nuclei are rare and the single cells are typically plasmacytoid unlike parathyroid lesions which have centrally located nuclei (Fig. 30.22). Insular carcinomas can be extremely difficult to distinguish from parathyroid proliferations. Both insular carcinoma and parathyroid proliferations have hypercellularity, abundant naked nuclei, loosely cohesive three dimensional groups, and pseudo-papillary architecture. While insular carcinoma has larger cells, the difference may be difficult to appreciate (Fig. 30.23). Necrosis may be present but would not exclude a malignant parathyroid proliferation.

While inconsistently present, the identification of distinct two cell population (chief cells and oxyphilic cells) in a hypercellular smear can be

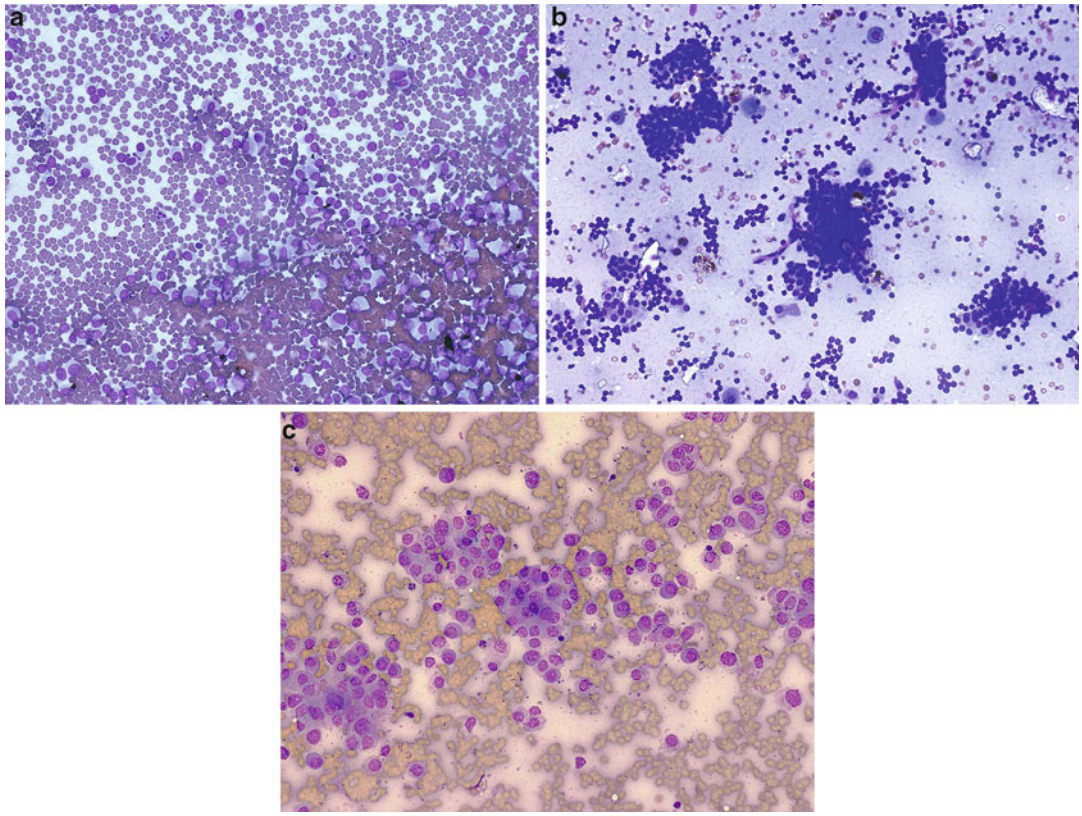

Fig. 30.22 Cytologic comparison of chief cell predominant parathyroid proliferations and medullary carcinomas. (**a**, **c**) Medullary carcinoma; (**b**) Parathyroid adenoma. Note that medullary carcinoma is more dyscohesive, has many single cells but few naked nuclei and has generally larger cells with more cytoplasm. Pseudopapillary architecture is uncommon in medullary carcinoma

very helpful in identifying parathyroid lesions, as most neoplastic follicular lesions are monomorphic (Fig. 30.20c). Despite the subtle cytologic differences between parathyroid and thyroid neoplasms, the distinction is often challenging, and a high index of suspicion may be the best safeguard against misdiagnosis.

Two cytologic variants deserve special mention because of their potential for misdiagnosis. Oxyphilic variants of parathyroid adenoma/carcinoma can be mistaken for follicular neoplasms, Hurthle cell neoplasm (Fig. 30.24) and Hashimoto's thyroiditis (Fig. 30.25) [100, 101]. The distinction between follicular neoplasm and oxyphilic parathyroid neoplasm can be quite difficult because both show syncytial three dimensional groups but abundant naked nuclei and pseudo-papillary architecture would favor the latter. While both Hurthle cells and oxphilic cells are true oncocytes and have densely granular cytoplasm, Hurthle cells have prominent nucleoli and sharply demarcated cytoplasmic borders and are most often arranged in cohesive sheets, whereas parathyroid oxyphilic cells lack nucleoli, have smaller nuclei, and have indistinct cytoplasmic borders resulting in a syncytial appearance. Again the presence of abundant naked nuclei and significant pseudo-papillary architecture are helpful in recognizing parathyroid neoplasms.

The distinction between oxyphilic neoplasms and Hashimoto's thyroiditis is based on the distinction between lymphocytes and naked epithelial nuclei. In Hashimoto's thyroiditis, the cellularity is composed of Hurthle cells, with large

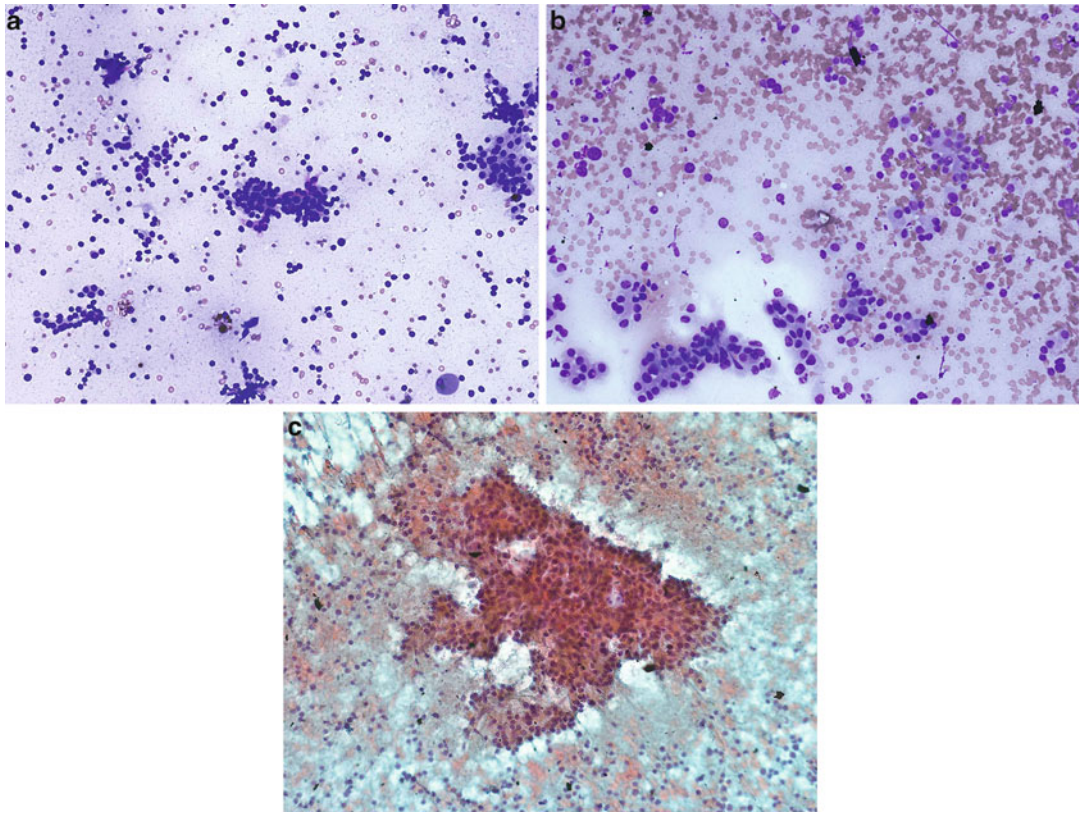

Fig. 30.23 Cytologic comparison between parathyroid proliferation and insular carcinoma. (**a**) Parathyroid adenoma; (**b**) Insular carcinoma on Difquik stain; (**c**) Insular carcinoma on Pap stain showing papillary architecture. Both lesions show numerous naked nuclei three dimensional groups and pseudopapillary architecture but insular carcinoma tends to have larger cells with more cytoplasm and larger nuclei

nuclei and lymphocytes with small nuclei, whereas in oxyphilic parathyroid proliferations, all the nuclei are from oxyphils so the size of the intact nuclei and the naked ones is roughly the same, in fact, the naked ones may be slightly larger. Pseudo-papillary architecture is also uncommon in Hashimoto's thyroiditis and should raise the possibility of a parathyroid proliferation.

Water-clear cell variants of parathyroid proliferations can closely mimic metastatic renal cell carcinoma as well as other clear cell lesions [102]. As these are very rare lesions and renal cell carcinoma is the most common metastasis to the thyroid, a history of renal cell carcinoma should be solicited for any clear cell lesion identified on "thyroid" FNA. However, in the absence of such a history, a serum PTH or needle washout for PTH may be helpful. Immunohistochemical studies may be useful if a cell block is available but FNAs of both the thyroid and parathyroid rarely yield sufficient material for these studies.

Given the difficulty of distinguishing parathyroid and thyroid neoplasms on cytology, it is prudent to treat all FNAs of the posterior thyroid as potential parathyroid aspirations. Additional information which may be helpful for diagnosis include: the exact location (upper, mid, or lower pole, posterior or anterior) of the lesion, its size, evidence of infiltration, serum calcium, serum PTH, serum calcitonin, renal status, and history of disease. If the cytologic appearance brings up the differential of parathyroid proliferation, it is advisable to recommend preoperative serum calcium, calcitonin, and PTH measurement as the results could dramatically affect clinical and surgical management.

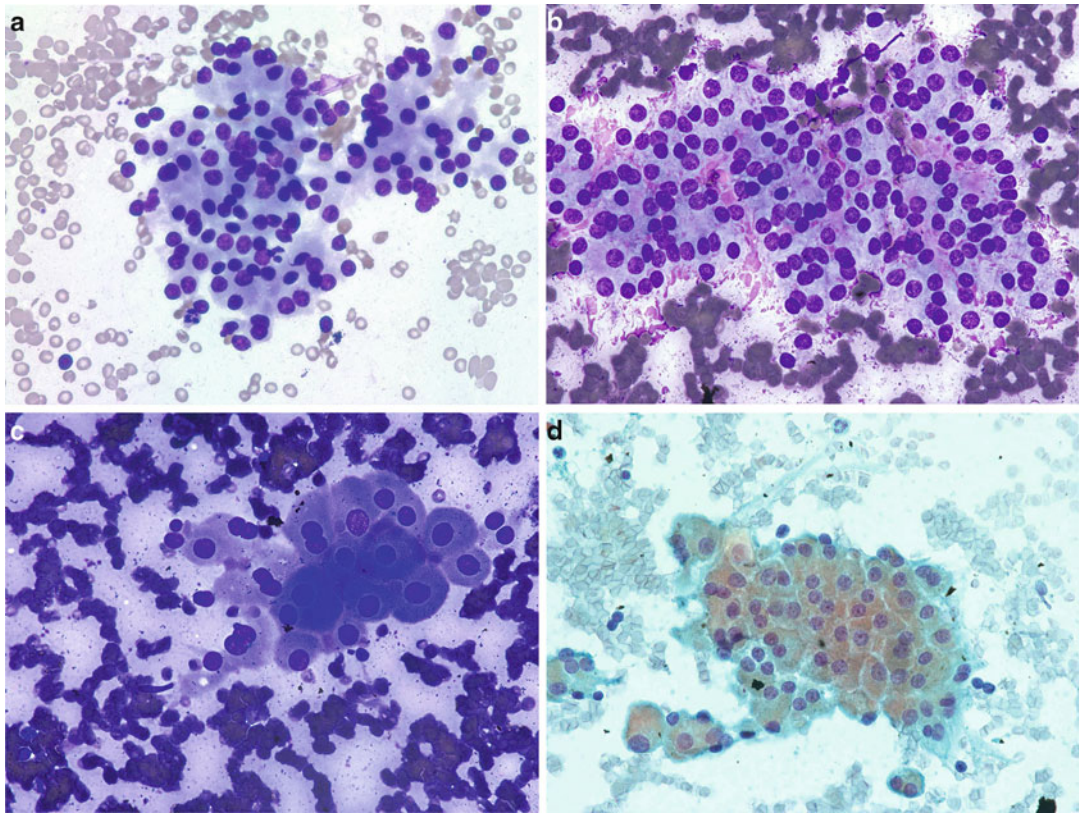

Fig. 30.24 Cytologic comparison between oxyphilic parathyroid proliferations and thyroid neoplasms. (**a**) Oxyphilic parathyroid proliferation and (**b**) Follicular neoplasm and (**c**, **d**) Hurthle cell neoplasm. The cellular groups in oxyphilic parathyroid proliferations can be very similar to those of follicular neoplasms but oxyphilic parathyroid neoplasms also tend to have pseudopapillary architecture and abundant naked nuclei (not shown), features lacking in follicular neoplasm. Hurthle cell neoplasms have much larger cells, sharp cytoplasmic borders, and prominent nucleoli (best seen on Pap stain), all features not seen in oxyphilic parathyroid neoplasms. Hurthle cell neoplasms also lack the abundant naked nuclei and pseudopapillary architecture (not shown)

The use of FNA to cytologically confirm putative parathyroid lesions has declined with the advent of more sensitive and specific radiologic techniques such as the sestamibi scan, but this approach is still sometimes used when a lesion cannot be reliably localized by these nuclear medicine techniques. Parathyroid adenomas that fail to localize by sestamibi are often small with predominant chief cell or significant stroma fat components. Other indications include failed previous exploration, previous neck surgery, radiation, and severe comorbidities [103]. Putative parathyroid lesions are identified by ultrasound and then aspirated. The cytologic features are as previously described, as are the caveats. FNA alone has a relatively low sensitivity but washout assays for PTH can improve both sensitivity and specificity [104, 105].

There is some debate whether parathyroid lesions should be aspirated at all. Rare instances of seeding of the needle track by parathyroid carcinoma have been reported [106, 107]. Additionally, florid biopsy site reactions can sometimes produce worrisome artifacts which can compromise the histologic evaluation for parathyroid carcinoma [108, 109] (Fig. 30.26). On the other hand, the largest study assessing the risk of parathyromatosis after FNA of parathyroid lesions showed no case of needle track seeding in 81 patients [103]. Furthermore, biopsy induced reactions usually have tell-tale features such as hemorrhage and foreign body giant cell reaction which persist for several weeks [109]. Given the generally short time between biopsy and excision, the distinction between artifact and invasion can usually be made. Given the very low but real

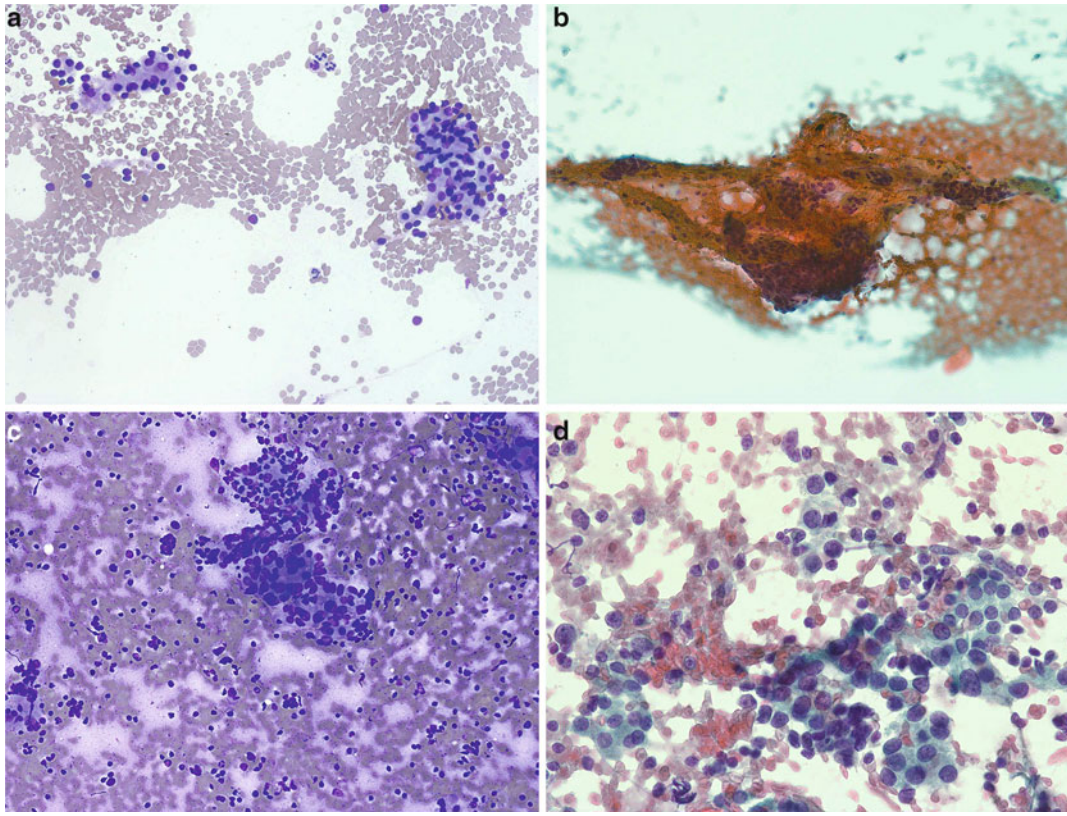

Fig. 30.25 Cytologic comparison between oxyphilic parathyroid proliferation and Hashimoto's thyroiditis. Oxyphilic parathyroid carcinoma on (**a**) Difquik stain and (**b**) Pap stain (200×); and Hashimoto's thyroiditis (**c**) Difquik stain and (**d**) Pap stain (400×). Note the nuclei of the lymphocytes are much smaller than those of the follicular cells, crush artifact is readily identified. The naked nuclei of oxyphilic parathyroid neoplasms are the same size or larger than the intact nuclei. Oxyphilic parathyroid neoplasms also have pseudopapillary architecture, which is not typically seen in Hashimoto's thyroiditis. In addition on pap stain the lymphocytes have a much coarser chromatin than the follicular cells or oxyphilic cells. Also, the cells in oxyphilic parathyroid neoplasms tend to be somewhat smaller than the follicular cells in Hashimoto's. This difference is less evident in this case because A is an oxyphilic parathyroid carcinoma which has somewhat larger nuclei than usual

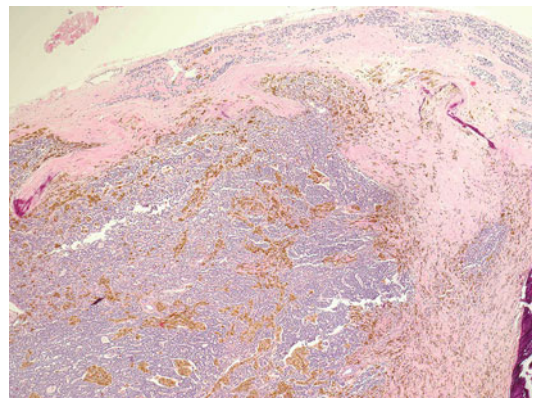

Fig. 30.26 Fine needle aspiration artifact showing typical hemorrhage and fibrosis. Giant cell reaction may also be present

risk of seeding and/or compromising histologic evaluation, a good middle ground position would be to avoid FNA in all parathyroid lesions which show worrisome clinical (marked hypercalcemia or markedly elevated PTH) or radiologic features (large size, irregular shape, invasion).

Intraoperative Frozen Section Evaluation

Intraoperative evaluation of parathyroid tissue is most commonly performed during parathyroidectomies for parathyroid proliferations or to identify a parathyroid for re-implantation during thyroid surgery. Prior to performing frozen sectioning, the location of the excised tissue, its size, its weight, and its gross appearance should be recorded. Inking is not generally necessary but if the differential includes parathyroid carcinoma, inking should be done to assess margins. The first goal of intraoperative evaluation is to determine if parathyroid tissue is present or not. This is important because on gross examination, lymph nodes, ectopic thymus, thyroid, and even fat are sometimes mistaken for parathyroid. Fortunately, the actual identification of parathyroid tissue is generally very accurate (>99%) [110]. However, diagnostic pitfalls do occur.

A common error is to confuse thyroid and parathyroid tissues [9, 111]. While typical parathyroid and thyroid tissues are not generally confused, solid patterns and clear cell change in thyroid tissue on one hand, and follicular architecture and oxyphilic cell predominance in parathyroid tissue on the other, can make the distinction challenging and occasionally impossible on frozen section (Fig. 30.27). Helpful clues for identifying parathyroid tissue include an overall

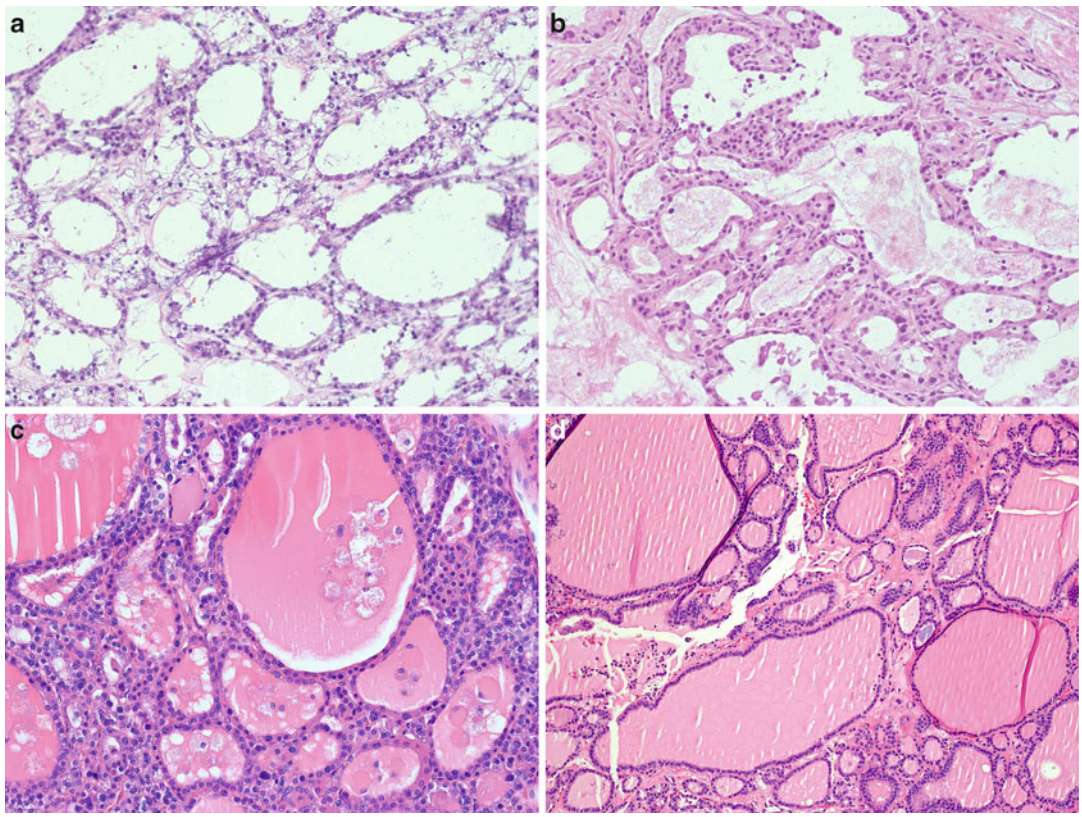

Fig. 30.27 Parathyroid tissue with follicular architecture mimicking thyroid. (**a**) Parathyroid adenoma with follicular architecture—frozen section; (**b**) Normal thyroid—frozen section. The distinction can sometimes be difficult even on permanent sections (**c**) Parathyroid adenoma with follicular architecture (**d**) Normal thyroid

organoid appearance (nests, cord, solid sheets), the presence of stromal fat, presence of other cell types (oxyphils, clear cells), and an adjacent rim of normal parathyroid. Useful clues to identify thyroid tissue include the predominance of follicular or microfollicular architecture, the presence of lymphocytes, the general absence of stromal fat, a single parenchymal cell type within the nodule and, in Hurthle lesions, the presence of prominent nucleoli. In difficult cases, the presence of polarizable birefringent oxalate crystals in thyroid tissue may often be helpful [112] (Fig. 30.28). While these are helpful characteristics, they are not absolute and definitive diagnosis may sometimes need to be deferred. In general, it is better to communicate uncertainty to the surgeon than to guess.

Another potential pitfall is to mistaken lymphoid tissue for parathyroid tissue (Fig. 30.29). In lymph nodes, the error usually occurs when there is freezing artifact which produces clefts that can resemble stromal fat or when there is fatty replacement of the lymph node [9, 111]. In thymus, natural fatty replacement during involution gives the lymphoid tissue an organoid appearance at low power. However, on closer examination, lymphocytes are much smaller, densely packed, and do not exhibit any true architectural organization whereas chief cells are larger, more widely and uniformly spaced and arranged in an organoid architectural pattern. Thus, these errors can be largely avoided with good frozen section technique and careful microscopic evaluation. An alternative means of identifying parathyroid tissue is the via aspiration and IOPTH assessment of the specimen [113].

Once the tissue has been confirmed to be parathyroid tissue, it should be assessed for parenchymal proliferation [9, 114]. The presence of proliferation is usually based on size, weight, hypercellularity, and intracellular fat content. Parathyroid glands weighing more than 50–70 mg and larger than 6-8 mm are generally considered abnormal. Care should be exercised when using the parameters of size and weight in this evaluation because specimens sometimes contain additional surrounding nonparathyroid tissue, usually adipose tissue but sometimes thyroid or lymphoid tissue, which contributes to the total size and weight of the specimen. Hypercellularity, as previously discussed, is a somewhat tenuous measure of hyperplasia. It is most useful when marked or when stromal fat is entirely absent but overall is a helpful confirmatory characteristic in enlarged glands. Due to the significant variability in normal fat content, extreme caution should be exercised in calling a normal sized parathyroid gland hypercellular in the face of normal serum calcium and PTH. Evaluation for the loss of intracellular fat is sometimes helpful in ambiguous cases. Loss of intracellular fat is evident in 80 % of parathyroid proliferations and should be

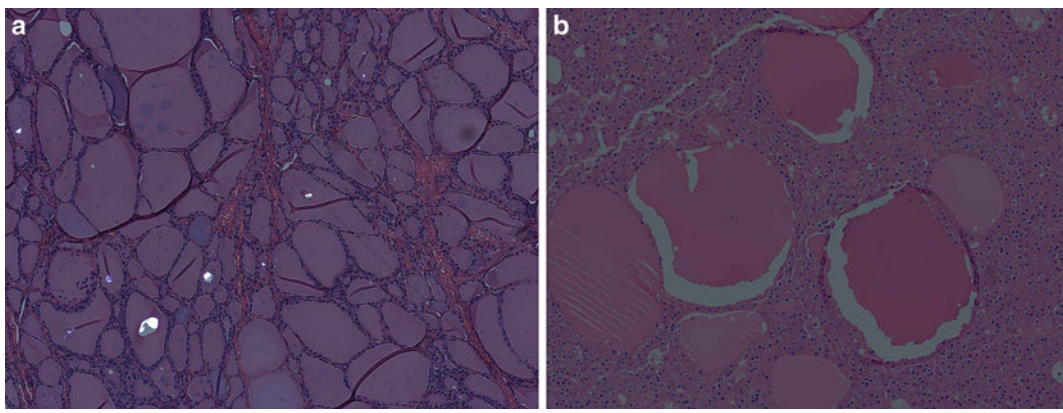

Fig. 30.28 Utility of polarization to distinguish thyroid and parathyroid tissues. (**a**) Birefringent oxalate crystals present in thyroid tissue; (**b**) Absence of birefringent oxalate crystal in parathyroid tissue with follicular architecture

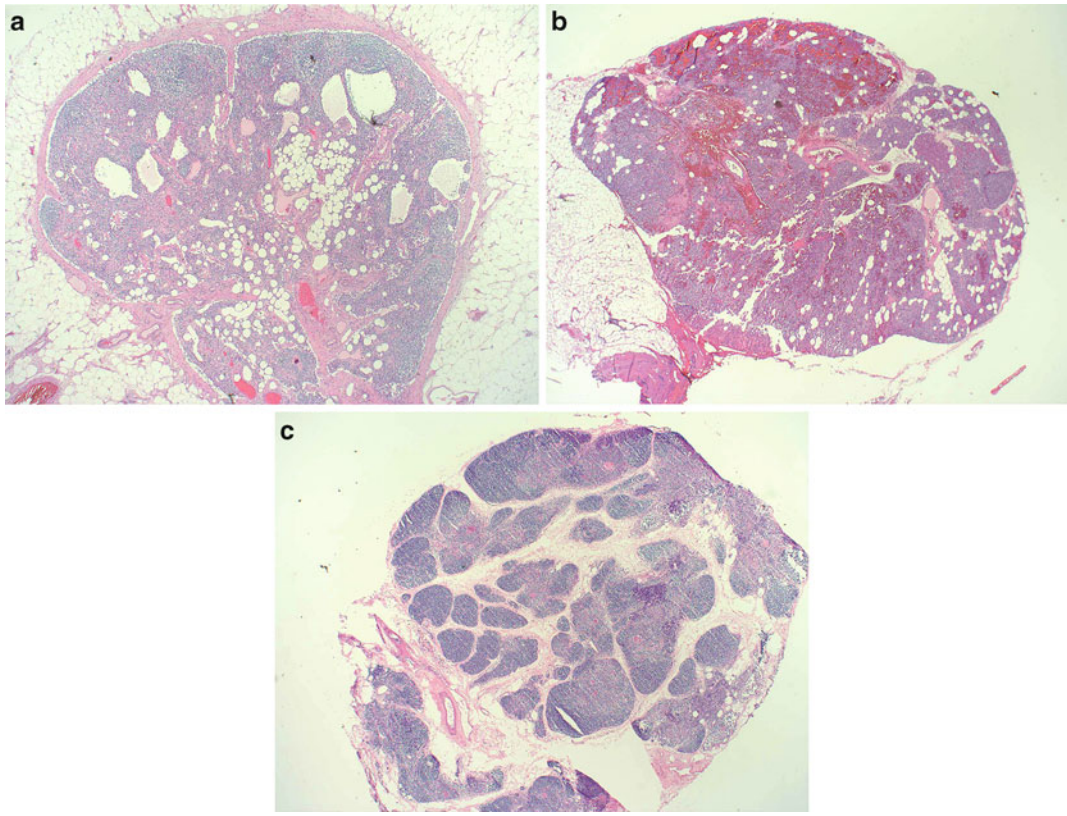

Fig. 30.29 Low power architectural mimics of parathyroid tissue. (**a**) Lymph node with partial fatty replacement; (**b**) Normal parathyroid; (**c**) Normal thymus

interpreted in conjunction with other characteristics. This evaluation can be readily and rapidly performed on frozen tissue using Oil red O, Sudan black or toluene blue stains [9, 110].

If the parathyroid tissue is determined to be proliferative, an attempt should be made to distinguish among hyperplasia, adenoma, and carcinoma. The presence of a rim of normal parathyroid is very helpful in making the diagnosis of adenoma but is only present in 60–70 % of cases. Likewise, the absence of stromal fat is also suggestive of adenoma. However, the diagnosis of adenoma rests on the identification of a normal parathyroid gland in addition to the abnormal proliferative parathyroid gland [110]. This diagnosis cannot be based solely on gross examination because many hyperplastic glands are not grossly enlarged. Parathyroid hyperplasias would of course be expected to show abnormalities in all four parathyroid glands. Historically, this determination has involved sampling of at least one of the "normal" appearing parathyroid glands in addition to the grossly enlarged one.

With the wide adoption of preoperative sestamibi localization of parathyroid lesions and implementation of the rapid intraoperative PTH assay, this additional sampling and in fact intraoperative frozen section for parathyroid surgery as a whole has declined [114–117]. Since the goal is to see a drop in serum PTH by half and into the normal range, it is likely that surgery will continue until sufficient parathyroid tissue is removed to achieve a euparathyroid state. In that case it is unclear if it matters from a clinical standpoint whether the remaining tissue is normal, adenomatous, or hyperplastic. This is fortunate given the poor concordance rate in the distinction between parathyroid hyperplasias and

adenomas [66]. However, given the potential for false positive drops in the rapid intraoperative PTH assay, either due to errors in the assay or as a result of intraoperative parathyroid "stunning," when available, intraoperative frozen section remains a viable tool to minimize the risk of failed parathyroidectomy, particularly in cases where preoperative localization is ineffective or surgical findings are discordant [114, 115].

One area in which intraoperative frozen section remains important is in the evaluation for parathyroid carcinoma. While there are often clues suggesting this diagnosis both clinically and radiologically, the initial diagnosis is frequently a histologic one. Clues suggesting the diagnosis of parathyroid carcinoma have been previously discussed and include fibrotic bands, trabecular architecture, mitotic activity, prominent nucleoli, and necrosis but a definite diagnosis of parathyroid carcinoma requires overt malignant characteristics such as lymphovascular invasion, capsular/soft tissue invasion, perineural invasion, or metastasis. Care should be taken not to over call artifacts associated with the prior FNA or prior neck surgery. To avoid this, a previous history of such procedures should be solicited prior to frozen evaluation or whenever the diagnosis of parathyroid carcinoma is entertained.

Summary

The parathyroid organ consists of four small ovoid glands composed of chief cells, their derivatives, and stromal fat. The stromal fat content can vary dramatically with age, sex, body habitus, race, and general health. Chronic parathyroiditis is rare and is either nonspecific or autoimmune in nature, although granulomatous parathyroiditis is associated with tuberculosis or sarcoidosis. Parathyroid cysts are developmental or degenerative in nature. Parathyroid hyperplasias involve all of the parathyroid glands whereas adenomas typically involve a single gland. Double adenomas are rare. Parathyroid adenomas and asymmetric hyperplasias cannot be reliably differentiated histologically. Atypical adenomas have worrisome features but lack overtly malignant features whereas parathyroid carcinomas have overt malignant characteristics. Cytologic evaluation of the parathyroid proliferations is complicated by misidentification of site and cytologic characteristics similar to lesions of the adjacent thyroid. Intraoperative frozen section evaluation is useful for identifying parathyroid tissue, evaluating for parenchymal proliferation and identifying parathyroid carcinoma but not in differentiating hyperplasias from adenomas.

Society Guideline: N/A

Best Practices: N/A

Expert Opinion

Understanding the basis and limitations of the pathologic evaluation of the parathyroid is crucial for clinical and surgical management. The strength of histology is in segregating the clearly benign, which represent the vast majority of parathyroid lesions, from the worrisome/malignant. However, histology is not particularly good at distinguishing adenomas from asymmetric hyperplasias or atypical adenomas from carcinomas. As such the specific final diagnosis often relies on clinical, radiologic, surgical, histologic, and immunophenotypic findings as well as close clinical follow-up.

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Parathyroid Carcinoma

31

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Contents

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Introduction

Parathyroid carcinoma is a rare endocrine malignancy and accounts for 0.7–5 % of all cases of primary hyperparathyroidism [1–3]. Due to its rarity, it is difficult to study and management is based on retrospective data from a limited number of small to moderately sized case series and cancer registry reports. There is still no consensus regarding several aspects of staging, management, and follow-up. Nevertheless, a busy endocrine surgeon is likely to encounter this disease at some point in their career and needs to be familiar with its presentation and management as these patients clearly do best if diagnosed preoperatively and managed accordingly. There have also been several developments in the understanding of the genetics of the disease in the last 15 years which have improved pathologic diagnosis as well as changes in the medical

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management of hypercalcemia which warrant review. This chapter will provide an overview of the latest in our knowledge of parathyroid carcinoma.

Epidemiology

The estimated prevalence of parathyroid carcinoma is around 0.005 % of all cancers [4]. It is now commonly estimated that it accounts for less than 1 % of cases of hyperparathyroidism [1, 5–7]. In older series that percentage ranged from 1 to 4 % [2, 3]; however, with the introduction of improved techniques for measurement of calcium and resulting increased recognition of cases of asymptomatic hyperparathyroidism, it is not surprising that a recent large meta-analysis has shown a rate of 0.74 % [1]. There have not been any differences demonstrated in parathyroid carcinoma with regards to gender, race, income level, or geographic region in the United States [4]. This is in contrast to the marked predominance of primary hyperparathyroidism in women. There appears to be an increased incidence of parathyroid carcinoma in Japan at 5 % in the older literature [3]. The incidence in China is similar to North America at 1 % [3]. The mean age of presentation is reported to be 55 years of age, which is a decade younger than that in patients with parathyroid adenomas [4, 8].

Pathology

The diagnosis of parathyroid carcinomas remains a challenge since they can grossly and microscopically mimic a parathyroid adenoma. Nevertheless, carcinomas are often firm, grayish white in color, and spherical in shape [5]. They may be surrounded by a thick capsule and are generally adherent or grossly invading into adjacent structures (Fig. 31.1). They range in size from 1.3 to 6.2 cm and weight between 600 mg–110 g, with a mean size of about 3 cm and weight of about 5–10 g [2, 8, 9].

Without evidence of metastatic disease or unequivocal invasion of adjacent structures, the histologic diagnosis of parathyroid carcinomas can be very challenging. The classic histopathology features as described by Schantz and Castleman [2] are listed in Table 31.1 and dem-

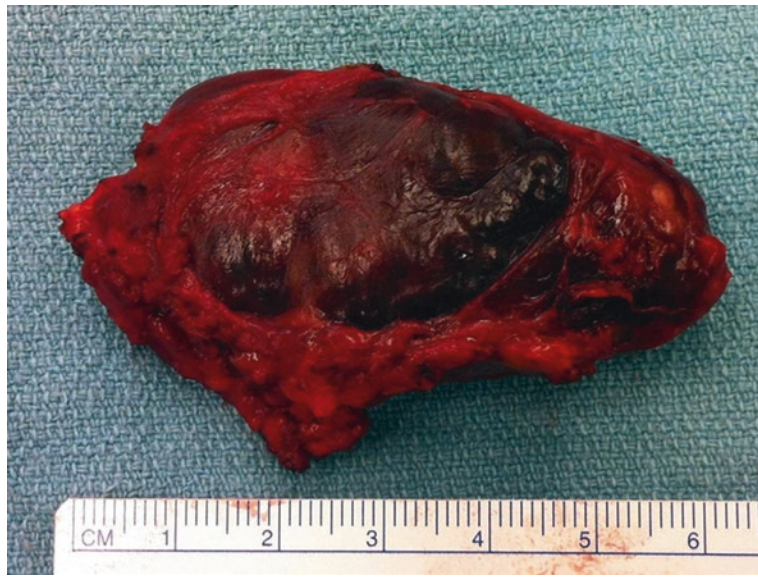

Fig. 31.1 Gross pathology specimen of a parathyroid carcinoma. The tumor was pushing and displacing the thyroid gland but not invading it. The right thyroid lobe was removed regardless due to a suspicious thyroid nodule which on final pathology was a papillary thyroid carcinoma. The recurrent laryngeal nerve was then seen draped over the tumor and the intervening tissues were dissected to the capsule to free the nerve and preserve it. The surrounding tissues were dissected en bloc

onstrated in Figs. 31.2, 31.3, 31.4, and 31.5. Also listed in Table 31.1 are their frequency as originally reported by Schantz and Castleman. None of the criteria are invariably found in every case and there are some nuances that can make their interpretation difficult. Schantz and Castleman felt that the presence of mitosis within parenchymal cells is the single most valuable criterion; however, this must be clearly distinguished from mitosis within endothelial cells. Similarly fibrosis must be distinguished from scarring from previous surgery. They felt that cellular atypia is not a useful distinguishing feature and more likely associated with adenoma. On the contrary, other authors have found mitosis not as helpful and nuclear atypia associated with carcinoma [10].

Table 31.1 Incidence of Shantz and Castleman histopathologic criteria in parathyroid carcinoma

Trabecular or rosette-like cellular architecture	90 %
Mitotic figures	81 %
Thick fibrous bands	80 %[a]
Capsular invasion	67 %
Vascular invasion	12 %

[a]From Bondeson et al. [10]. Rest of incidence data from Shantz and Castleman [2]

The challenge pathologists have faced with making this diagnosis is exemplified by a 1992 study where tumors were reclassified based on future malignant behavior such as recurrence and metastasis and less than half had been originally correctly diagnosed based on clinical and pathologic criteria alone [9]. These difficulties led the World Health Organization in 2004 to recommend that the diagnosis of parathyroid carcinoma be reserved for cases where there is unequivocal evidence of invasive growth or metastasis [11]. Tumors which have all of the classic features of parathyroid carcinoma but lack evidence of vascular, perineural, or full-thickness capsular invasion or metastasis should be classified as atypical parathyroid adenomas. This has been supported by a study in 2007 of 27 previously diagnosed parathyroid carcinoma patients which were reclassified based on the WHO criteria [12]. 59 % of the patients were reclassified as benign and none of these patients recurred at a median follow-up of 91 months.

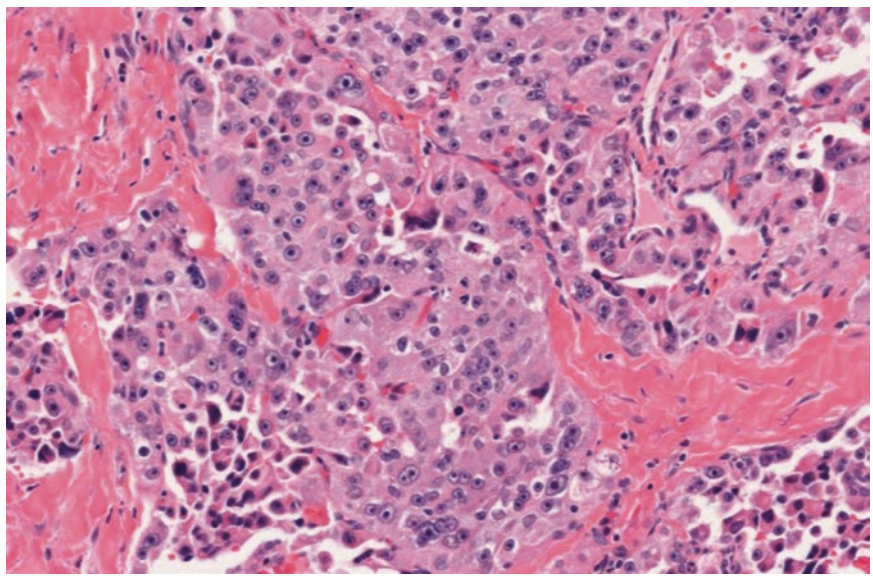

Fig. 31.2 Parathyroid carcinoma with pleomorphic nuclei, macronucleoli, mitoses, and thick fibrotic bands between nests and trabeculae of tumor. This tumor weighed 73.35 g and measured 9.6 cm × 5.3 cm × 4.4 cm. It invaded through the capsule and into fibroadipose tissue and extended to the resection margin. It showed necrosis, large acellular fibrous bands, vascular space invasion, and perineural invasion (H&E, 200× magnification)

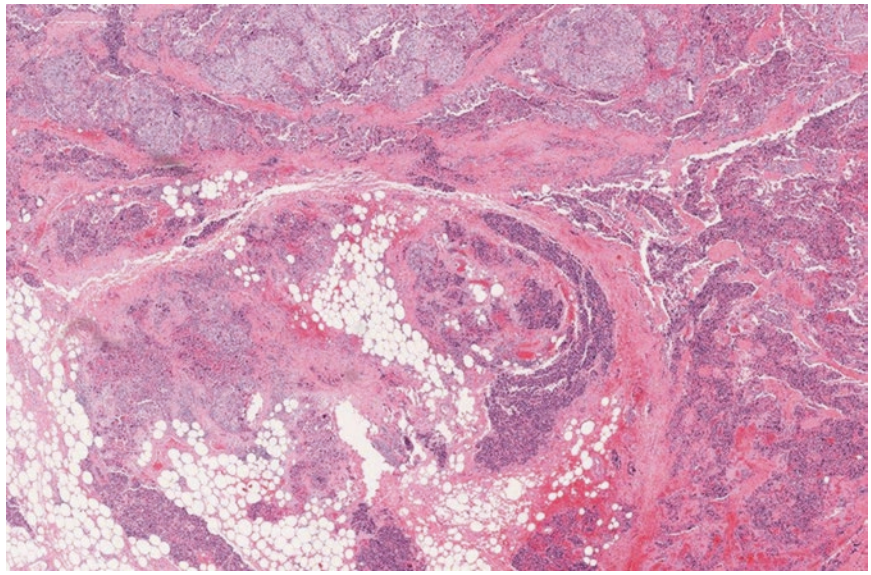

Fig. 31.3 Invasion into adjacent fibroadipose tissue. (H&E, 20× magnification)

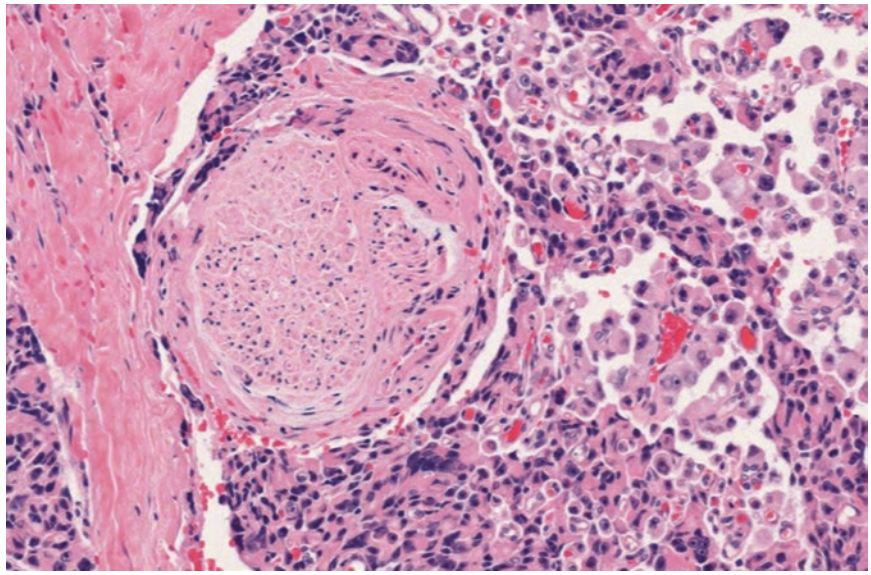

Fig. 31.4 Perineural invasion. (H&E, 200× magnification)

There is increasing evidence that immunohistochemistry techniques can substantially aid in the diagnosis of parathyroid carcinoma and may be considerably more accurate than histopathology using hematoxylin and eosin staining alone [13, 14]. As discussed earlier, the mitotic activity of parathyroid carcinomas compared to adenomas is controversial but generally thought to be higher. Similarly, analysis of cellular proliferation fractions using Ki-67 antibody labeling has generally shown higher values in carcinomas than adenomas but there are equivocal cases [15, 16].

Much more promising are targets within the cyclin D1-CDK4/6 pathway of retinoblastoma protein (Rb) phosphorylation which allows for cell cycle progression, (Fig. 31.6). This is now

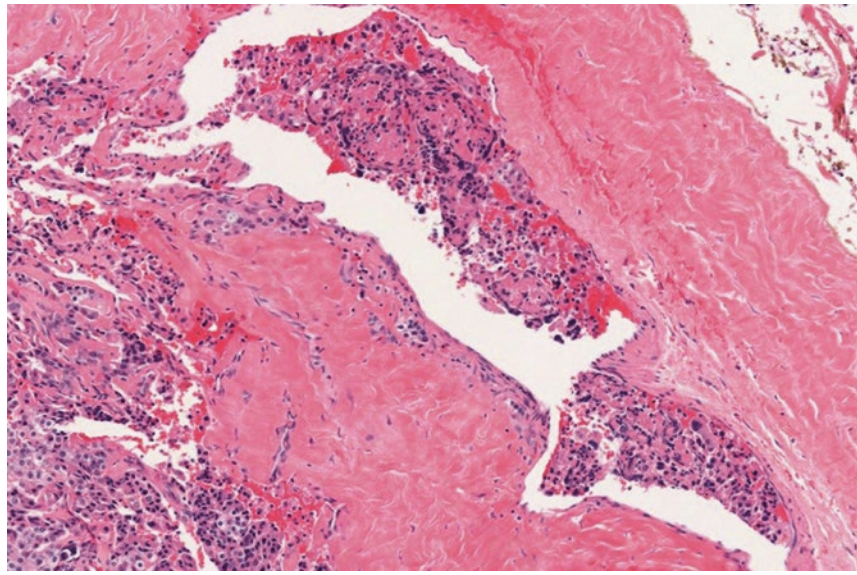

Fig. 31.5 Vascular space invasion. (H&E, 100× magnification)

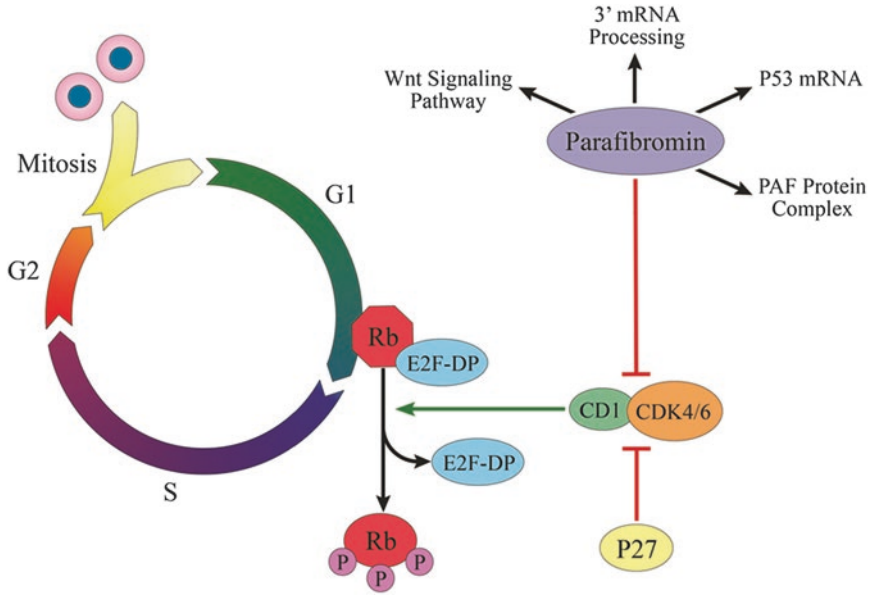

Fig. 31.6 Diagram of parafibromin's mechanisms of action in parathyroid tumorigenesis. Parafibromin is the protein product of the hyperparathyroidism-2 gene (HRPT2) otherwise known as cell division cycle 73 (CDC73) [17]. It is known to be mutated in over 95% of parathyroid carcinomas [18]. When mutated, it fails to inhibit the cyclin D1-cyclin dependent kinase 4/6 (CD1-CDK4/6) complex from phosphorylating the retinoblastoma (Rb) protein, which allows the cell to progress from growth 1 (G1) phase to synthesis (S) phase in the cell cycle [66]. It is also known to affect the wingless type (Wnt) signaling pathway which regulates multiple cellular process including cell fate specification, cell proliferation, and cell migration [15]. Loss of the Wnt pathway tumor suppressor protein adenomatous polyposis coli (APC) has been shown to have very high specificity for parathyroid carcinoma [23]. It also facilitates 3′ mRNA processing, known as polyadenylation, which protects mRNA from enzymatic degradation [17]. This is one mechanism by which it affects p53 as well as possibly a direct interaction with p53 mRNA [72]. It is also a component of the polymerase associated factor (PAF) protein complex which associates the RNA polymerase II subunit with histone methyltransferase complex and has multiple effects on gene transcription and potentially tumorigenesis [17]. P27 is also known to inhibit CD1-CDK4 and is frequently absent on immunohistochemistry of parathyroid carcinoma [16, 19]

known to be a key mechanism in parathyroid cancer pathogenesis [6]. Parafibromin, the protein product of HRPT2, a tumor suppressor gene mutated in hyperparathyroidism-jaw tumor syndrome, is a strong inhibitor of cyclin D1 amongst other functions which can potentially drive tumorigenesis [15, 17]. When the gene is mutated, it leads to Cyclin D1 overexpression which drives the pathway forward and leads to cell cycle progression. Partial or complete loss of immunohistochemical staining for parafibromin is highly specific (99 %) and sensitive (96 %) for parathyroid carcinoma [18]. However, this is dependent on how partial loss of immunohistochemical staining is interpreted which adds subjectivity to the test [15]. Cyclin-dependent kinase inhibitor 1B (Cdkn1b or $p27^{Kip1}$) is another inhibitor of the cyclin D1-CDK4 complex [19]. Absence of p27 expression has been shown to have a sensitivity of 83 % and specificity of 100 % for parathyroid carcinoma in one study [16]. In the same study, absence of immunohistochemical staining for Rb had a sensitivity of 94 % but specificity of only 65 % for parathyroid carcinoma.

There are several other markers from alternative pathways that have been targeted by immunohistochemistry techniques to aid in diagnosis. Ubiquitin carboxy-terminal esterase L1 (UCHL1), also known as protein gene product 9.5, is abundantly present in all neurons and is also highly specific to neuroendocrine cells [20]. Strong staining has been shown to have a sensitivity of 78 % and specificity of 100 % for parathyroid carcinoma [21]. Positive staining for galectin-3, a lectin expressed in several malignant tumors, has been shown to have a sensitivity of 92 % and specificity of 97 % for parathyroid carcinoma [22]. Loss of the adenomatous polyposis coli (APC) gene, part of the Wingless type (Wnt) pathway which is functionally linked to parafibromin, has also been implicated in parathyroid carcinomas but not typical adenomas [15]. It has been shown to have a sensitivity of 75 % and specificity of 100 % for parathyroid carcinoma [23]. Although, it is also frequently absent in atypical adenomas, it is present even in HRPT2 adenomas with absent parafibromin expression [24]. All of these markers have considerably improved pathologists ability to make the correct diagnosis.

Clinical Presentation

While most parathyroid adenomas are found incidentally and patients only endorse mild neurocognitive symptoms, patients with parathyroid carcinoma usually present with significant signs and symptoms of hypercalcemia and at times hypercalcemic crisis [3, 8, 25–27]. These signs and symptoms are listed in Tables 31.2 and 31.3 along with their frequency.

Hypercalcemic crisis, also termed parathyrotoxicosis, is a life-threatening condition associated with critically elevated calcium levels >16 mg/dl and characterized by acute renal failure and severe neurologic manifestations of profound weakness, somnolence, and even coma [5]. About 10 % of patients present in this manner [3]

Table 31.2 Incidence of symptoms at presentation

Fatigue	57 %
Bone pain	51 %
Headaches	26 %
Anorexia	25 %
Joint pain	22 %
Dyspepsia	20 %
Memory deficit	20 %
Weight loss	15 %
Muscular pain	15 %
Paresthesias	11 %
Constipation	7 %
Polyuria	7 %
Polydipsia	7 %
Neck pain	4 %
Asymptomatic	30 %

Table 31.3 Incidence of signs and associated conditions at presentation

Renal disease	40 %
Bone disease	34 %
Palpable neck mass	34 %
Urolithiasis	31 %
Weight loss	21 %
Peptic ulcer	8 %
Pancreatitis	6 %
Hoarseness	1 %
Hypercalcemic crisis	8 %
Asymptomatic	2 %

and they require urgent treatment of their hypercalcemia as is discussed later.

A palpable neck mass associated with symptomatic primary hyperparathyroidism is the classic, pathognomonic presentation for parathyroid carcinoma but only occurs in about a third of patients in modern series [3]. Nevertheless, very rarely do patients present without any signs or complications of hypercalcemia as listed in Table 31.3 [3, 27]. These findings in a patient with significant hypercalcemia should alert the physician to the possibility of parathyroid carcinoma as they proceed with further workup. As will be discussed later in this chapter, the surgical approach to parathyroid carcinoma is fundamentally different from parathyroid adenoma. The minority of patients in whom there is high clinical suspicion for parathyroid carcinoma preoperatively, undergo en bloc surgical resections and have better outcomes than when the diagnosis is made on final pathology [28].

Less than 10 % of patients have nonfunctional parathyroid carcinomas and they often present late from mass affect unless found incidentally [29]. Symptoms may include hoarseness, dysphagia, or even dyspnea and indicate advanced invasive disease.

Workup

Laboratory Findings

Patients with parathyroid carcinoma present with mean calcium levels around 13.5–14 mg/dl (about 3.5 mmol/l) but can range from 8.8 to 24 mg/dl (2.2–6 mmol/l) [25, 27, 30]. About a third of patients present with severe hypercalcemia (>13.5 mg/dl), a third moderate hypercalcemia (12–13.5 mg/dl), and a third mild hypercalcemia (<12 mg/dl) [25]. Mean PTH levels from Talat's and Shulte's review of the literature (205 patients) were on average 8.7 times the upper limit of normal (566 pg/ml, 60 pmol/l) with a range from 1 to 71.6 times the upper limit of normal (65–4660 pg/ml, 6.9–494 pmol/l) [30]. A PTH level 10 times the upper limit of normal has a positive predictive value of 84 % for the diagnosis of parathyroid carcinoma [31].

Imaging

Imaging plays a fundamentally different but equally important role in parathyroid carcinoma as compared to benign parathyroid disease. The goal is not only to identify which side the tumor is on, which is usually readily apparent, but more so the presence and extent of local invasion and any associated regional and distant metastases. In the vast majority of cases, the diagnosis of malignancy is uncertain or not even suspected and imaging can provide clues that point towards an invasive process. There are a variety of functional and anatomic imaging modalities that can be used for suspected cases of parathyroid carcinoma and a thorough workup should include both types.

The functional imaging modality most frequently used in benign parathyroid disease (and often the only modality) is technetium-99 m sestamibi scanning with or without single-photon emission tomography (SPECT). This is also useful in malignant disease not only to identify the primary lesion but also any regional or distant metastasis [27]. Positron emission tomography (PET) can also be used to characterize the primary and identify regional and distant metastasis and can be complimentary [32, 33]. There have been reports of metastatic lesions that were nondetectable on technetium-99m sestamibi scanning but localized with PET [33], and vice-versa [34].

Anatomic imaging has a more critical role in surgical planning in parathyroid cancer. Cervical ultrasound is often the first modality employed especially in patients that present with a neck mass. Ultrasound has a very high accuracy at detecting parathyroid glands the size of carcinomas and certain sonographic features can be very suggestive of malignancy [27, 35]. These features include a large hypoechoic gland, lobulated appearance, indistinct margins, calcification, abnormal vascularity, and a thick capsule [36, 37]. Figure 31.7 shows an example with some of these features. Ultrasound can also identify potentially involved structures; however, this is probably best demonstrated with computed tomography (CT) or magnetic resonance imaging (MRI), one of which is essential for adequate preoperative preparation. Figure 31.8 shows the CT of the

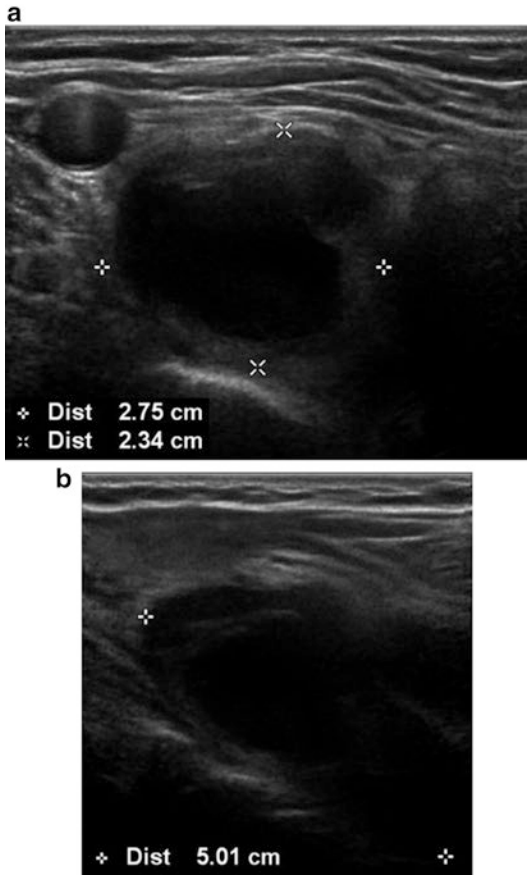

Fig. 31.7 Preoperative axial (**a**) and sagittal (**b**) ultrasonography images of the parathyroid carcinoma from Fig. 31.1. Note the lobulated, indistinct margins and thick capsule

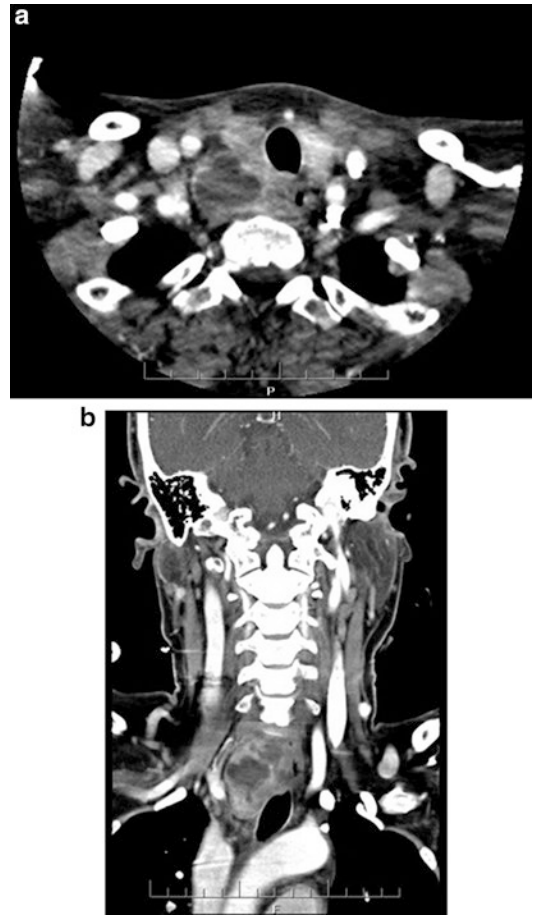

Fig. 31.8 Preoperative axial (**a**) and sagittal (**b**) contrast-enhanced computed tomography images of the parathyroid carcinoma from Fig. 31.1. Note the displacement of the surrounding tissues

same patient as in Fig. 31.7. These modalities can help the surgeon formulate a surgical plan in advance should invasion of critical structures such as the esophagus or trachea be seen and thereby help him or her achieve an en-bloc resection.

Needle biopsy of a primary parathyroid lesion suspicious for parathyroid carcinoma is not recommended primarily due to high nondiagnosis rate [38]. There have also been two case reports of potential tumor seeding along FNA tracks [39, 40]. In cases of recurrence, needle biopsy of suspicious lesions can help localize and confirm the site of recurrence [38].

Physical Examination

A comprehensive head and neck examination is vital in the workup of parathyroid carcinoma as a high percentage of patients will present with a palpable neck mass. A mass that feels fixed to adjacent tissues provides important information that will aid in surgical planning. In addition, flexible endoscopic examination of the vocal folds should be strongly considered as this can alert the surgeon to recurrent laryngeal nerve involvement which can also greatly facilitate decision making at the time of surgery.

Differential Diagnosis

The differential diagnosis for patients presenting with primary hyperparathyroidism and findings suggestive of malignancy such as a neck mass includes the very unusual situation of parathyroid adenoma or hyperplasia with a concomitant head and neck malignancy. Malignancies that present with central neck metastasis, most commonly papillary thyroid carcinoma and squamous cell carcinomas of the laryngopharyngeal tract could conceivably be mistaken for a parathyroid carcinoma. This should be distinguishable by imaging characteristics, endoscopic examination, and lower calcium and PTH levels.

A more common situation is a patient who was thought to have a parathyroid adenoma or an atypical parathyroid adenoma but presents several years later with multiple functioning parathyroid nodules in the superficial and deep soft tissues of the neck, termed parathyromatosis [41]. This may be very difficult to distinguish from locoregional recurrence of a mistaken parathyroid carcinoma. Parathyromatosis is usually seen after surgery for parathyroid adenoma and is thought to be the result of tumor spillage and reimplantation. It usually has a characteristic distribution in the previous surgical bed and along the incision; however, at times it can appear to extend outside the previous surgical field. There have also been reports of de novo parathyromatosis in patients who have not undergone surgery [41]. This is postulated to be the result of an overgrowth of embryologic rests of parathyroid tissue.

As previously discussed, atypical parathyroid adenomas are parathyroid tumors that show the same characteristics of parathyroid cancer but not unequivocal evidence of invasion. When distant metastasis occur in this situation, the diagnosis of carcinoma becomes clear.

Despite the difficulties arising from all of the entities sharing overlapping histopathologic features, they can often be differentiated based on clinical presentation. Parathyroid carcinoma usually presents with much higher calcium levels and associated end organ damage [41]. Nevertheless, there are no absolute clinical or histopathologic findings other than invasion. With identification of the HRPT2 mutation and its almost exclusive presence in parathyroid carcinoma, these lesions may become easier to characterize [13]. There have been several examples of incorrectly diagnosed atypical parathyroid adenomas that have later metastasized that would have been correctly identified with HRPT2 mutation testing [13].

Staging

There is no widely accepted staging system for parathyroid carcinoma. Shaha and Shah proposed a staging system in an editorial in 1999 following the TNM format (Table 31.4) and based on findings from a National Cancer Data Base (NCDB) study by Hundahl et al. [4, 42]. This study of 286 cases was the largest reported cohort of parathyroid cancer patients at the time and the first registry type study for parathyroid cancer. The staging system used a 3 cm cutoff to separate T1 and T2 patients based on the mean size of tumors found in the NCDB study as well as lymph node status to define stage III disease. However, these criteria were used despite a clear finding in the NCDB study against them acting as significant prognostic factors.

Table 31.4 Shaha and Shah staging system

T1	Primary tumor <3 cm
T2	Primary tumor >3 cm
T3	Primary tumor of any size with invasion of the surrounding soft tissues (i.e. thyroid gland, strap muscles, etc)
T4	Massive central compartment disease, invading the trachea or the esophagus, or recurrent parathyroid carcinoma
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M0	No evidence of distant metastasis
M1	Evidence of distant metastasis
Stage I	T1N0M0
Stage II	T2N0M0
Stage III	
a	T3N0M0
b	T4N0M0
c	Any T, N1, M0
Stage IV	Any T, Any N, M1

Table 31.5 Talat and Shulte staging system

Shulte a	Shulte b	
T1	Low	Evidence of capsular invasion
T2	"	Invasion of surrounding soft tissues, excluding the vital organs (trachea, larynx, and esophagus)
T3	High	Evidence of vascular invasion
T4	"	Invasion of vital organs (hypopharynx, trachea, esophagus, larynx, recurrent laryngeal nerve, carotid artery)
N0		No regional lymph node metastasis
N1	High	Regional lymph node metastasis
M0		No evidence of distant metastasis
M1	High	Evidence of distant metastasis
Stage I	Low	T1N0M0 or T2N0M0
Stage II	High	T3N0M0
Stage III	"	T4N0M0 or Any T, N1, M0
Stage IV	"	Any T, Any N, M1

More recently, Talat and Shulte proposed a different TNM type staging system which excluded size as a criterion and placed more emphasis on vascular invasion (Shulte a, Table 31.5) [30]. They also proposed a simpler low/high risk stratification system (Shulte b, Table 31.5) which essentially defined Shulte a stage I disease as low risk and stages II to IV as high risk. Both of these systems were then evaluated in a systematic review of the literature that included 706 patients which found them to be significantly related to risk of recurrence and death [30]. They further verified these two staging systems in a multi-institutional study of 82 patients which confirmed significant differences in recurrence and survival between low-risk and high-risk groups, as well as between stage I and II/III disease [43]. There were no significant differences seen between stage II and III disease, only 2 recurrences in the low risk group and no deaths in this study.

The Shaha and Shulte staging systems were recently further compared by the Spanish Parathyroid Carcinoma Study Group (SPCSG), a multi-institutional cancer registry in Spain [44].

Table 31.6 Recurrence and survival by stage

Stage	5 Year recurrence		5 Year survival	
	Shaha (%)	Shulte (%)	Shaha (%)	Shulte (%)
I	45	8	73	96
II	85	40	45	73
III	30	52	87	78
IV	67	67	33	33
Low risk		8		96
High risk		44		73

This prospectively collected registry study of 62 patients again demonstrated significant differences in recurrence and survival only between stage I and III patients in both staging systems.

The recurrence and survival data for the Shaha and Shulte staging systems based on Talat and Schulte [30] systematic review is listed in Table 31.6 [30]. As is clearly evident, we do not have a reliable multistage TNM type staging system and can differentiate between high and low risk disease.

Genetic Testing

The link between parathyroid cancer and hyperparathyroidism-jaw tumor syndrome HPT-JT is now clearly established [13]. Fifteen percent of patients with HPT-JT will develop parathyroid cancer in their lifetime [11]. This realization led to the discovery of the HRPT2 tumor suppressor gene (now officially named CDC73) in 2002 by Carpten and colleagues in 14 families with HPT-JT [45]. The gene codes for the parafibromin protein, so named for its relationship to parathyroid disease and fibro-osseous lesions of the jaw. The HRPT2 mutation is highly specific for parathyroid carcinoma, occurring in 77 % of tumors with confirmed malignant behavior and is rarely seen in adenomas and hyperplasia [13]. In fact, loss of parafibromin expression correlates with recurrence in tumors that contain some histopathologic features of parathyroid carcinoma but lack unequivocal evidence of invasion necessary to meet WHO criteria for malignancy [14].

The incidence of a germline HRPT2 mutation in apparent sporadic cases of parathyroid carcinoma is about 30 % [46]. Therefore, about a third of patients with parathyroid carcinoma have unrecognized HPT-JT despite no family history of the disorder. This has led some authors to recommend genetic testing for all patients with parathyroid carcinoma [46]. Unfortunately, sequencing the HRPT2 is currently expensive and many of the mutations are large deletion mutations that require gross deletion analysis to detect [13]. As discussed earlier, there is a monoclonal antibody to parafibromin used for immunohistochemistry which can confirm malignancy and triage patients for germline mutation testing. However, it requires a great deal of technical expertise to employ successfully and there are mixed results in the literature [13]. Hopefully, 2nd and 3rd generation sequencing will make identification of the mutation more accessible.

Management

The mainstay of management of parathyroid carcinoma and the only potential for cure is complete en-block surgical resection. The benefit of adjuvant radiotherapy is still not clear and experience with chemotherapy is limited. As en-block surgical resection is not the approach for parathyroid adenoma, the best outcomes are achieved in patients in whom there is a high preoperative suspicion for parathyroid carcinoma due to the signs, symptoms, laboratory and imaging findings outlined earlier in the chapter. Appropriate preoperative preparation is essential and includes appropriate imaging as well as correction of markedly abnormal electrolytes and fluid status.

Correction of Hypercalcemia

Seven to twelve percent of patients with parathyroid carcinoma will present with severe hypercalcemia and resultant organ dysfunction including renal failure and encephalopathy [5]. Although, these derangements will reverse with surgery, to minimize anesthetic risks, extreme hypercalcemia and dehydration must be corrected first and surgery should not be done on an emergency basis [6, 47]. The first line method to reduce serum calcium levels in any patient is dilution with isotonic IV fluids [48]. This will correct dehydration and improve renal function thereby increasing excretion of calcium. A drop in serum calcium of 1–2 mg/dl (0.3–0.5 mmol/l) can be expected [48]. One currently recommended regime is to start isotonic saline at an initial rate of 200–300 ml/h and then titrate to maintain a urine output of 100–150 ml/h [49].

In patients with underlying heart failure or renal disease, the addition of loop diuretics may be necessary to prevent fluid overload [49]. In the past, aggressive IV fluid hydration combined with intensive loop diuretic therapy was recommended for all patients. This has largely fallen out of favor as it requires very close ICU monitoring for fluid overload and electrolyte replacement [47, 48, 50]. There are now several medication options which simplify the control of hypercalcemia. The first line agents are calcitonin, bisphosphonates and cinacalcet and they are best used in combination to decrease calcium quickly and maintain a durable effect [48].

Calcitonin is the fastest acting calcium lowering agent and its most potent form is derived from salmon. It increases renal calcium excretion and decreases bone resorption by interfering with osteoclast function. It acts within 4–6 h but will only decrease calcium 1–2 mg/dl (0.3–0.5 mmol/l). Adverse effects are limited to mild nausea and rare hypersensitivity. Tachyphylaxis usually develops by 48 h so other medication must be started concurrently such as bisphosphonates to maintain normocalcemia [48].

Bisphosphonates such as pamidronate or zoledronic acid also inhibit osteoclast mediated bone resorption. They take longer to achieve effect then calcitonin (2–4 days) but they are much more potent. They are also relatively nontoxic. Osteonecrosis of the mandible can occur with repetitive high IV dosing but this is only a concern with long-term therapy [48].

Cinacalcet, a calcimimetic drug, is a medication that is specifically used in cases of parathyroid related hypercalcemia. It binds calcium

sensing receptors on parathyroid cells, and through allosteric activation, decreases parathyroid hormone secretion by enhancing negative feedback. It has a specific indication for parathyroid carcinoma in addition to primary hyperparathyroidism in patients unable to undergo parathyroidectomy and secondary hyperparathyroidism with renal failure. Its primary use is for long-term management of hypercalcemia but it can also be used in the acute setting [51]. Unfortunately, adverse effects such as nausea, vomiting, headache, and dehydration are fairly common [48].

There are several other medications which can decrease serum calcium levels but are not frequently used in the setting of parathyroid carcinoma. Glucocorticoids will decrease dietary calcium absorption by decreasing calcitriol production. Denosumab is another potent inhibitor of bone resorption which is sometimes used in the long-term management of hypercalcemia refractory to bisphosphonates. Other medications previously used for hypercalcemia such as mithramycin, phosphates, and gallium nitrate are now rarely used due to unfavorable side effect profiles [48].

Anesthetic Considerations

Once fluid status and electrolytes have been corrected, the patient can be safely brought to the operating room [52]. Timely surgical resection is important as it will lead to a rapid correction of parathyroid hormone level and electrolytes thereby reducing fluid requirements as well as reversing neurocognitive symptoms [25, 48]. Nevertheless, there are some important considerations for the anesthesiologist during the surgery. These include maintaining hydration, careful use of muscle relaxants if there is already muscle weakness from the hypercalcemia, and careful monitoring of the echocardiogram for shortened PR or QT intervals which can lead to ventricular arrhythmias [47, 52].

Surgical Approach

Surgery should be performed with the goal of complete en-block resection. This offers the best potential for cure [28]. Preoperative imaging is essential and can help identify potentially involved structures and avoid surprises during surgery [27]. Involved structures should be resected en-bloc with the specimen to ensure negative margins. Rupture of the capsule should be avoided if at all possible to prevent tumor spillage as parathyroid tissue is known to easily re-implant and this may contribute to the high risk of recurrence [6, 27]. The most common sites of invasion include the ipsilateral thyroid gland (89%), strap muscles (71%), ipsilateral recurrent laryngeal nerve (26%), esophagus (18%) and trachea (17%) [3]. Ipsilateral thyroid lobectomy was routinely recommended in the past [27], based on correlation with survival and recurrence on multivariate analysis in an early study [9]; however, two recent series do not demonstrate any advantage with prophylactic thyroidectomy unless there is clear thyroid invasion [25, 38]. During dissection, the recurrent laryngeal nerve can be draped over or under the tumor and should be carefully identified and preserved if not involved [25]. If the nerve is clearly involved by tumor it will need to be sacrificed and often the length of segment lost precludes primary anastomosis. If the distal stump can be identified, neurorrhaphy to the ansa cervicalis for maintenance of tone in the paralyzed vocal fold usually leads to acceptable voice outcomes [53].

Ipsilateral central or lateral neck dissection should be performed if preoperative imaging or intraoperative findings suggest lymph node involvement. Lymph node involvement at the time of presentation is highly unusual in recent series on parathyroid carcinoma [25, 28]. The rate of lymph node involvement in large cancer registry studies is between 2 and 15% of the minority of cases for which lymph node status is reported [4, 54, 55]. The levels of involved nodes are not reported in the large series and the small series have too few to draw any conclusions. Due to the rarity of lymph node involvement, prophylactic central or lateral neck dissection is controversial but not recommended by most authors, as it is unlikely to reduce the risk of recurrence but may result in morbidity [5, 6, 25, 56].

Some surgeons advocate intraoperative parathyroid hormone monitoring to rule out concomi-

tant parathyroid adenomas or hyperplasia and ensure complete removal of abnormal parathyroid tissue [5]. There have been reports of parathyroid carcinoma in the setting of bilateral parathyroid hyperplasia [57]. The utility and reliability of this approach in the setting of very high levels of parathyroid hormone from carcinoma is unknown. Furthermore, the potential risk of parathyromatosis from seeding the contralateral side during 4 gland exploration likely outweighs any benefit.

A high preoperative clinical suspicion for parathyroid carcinoma offers the best potential for performing the appropriate surgical treatment [25], unfortunately, for the vast majority of patients the diagnosis is not made or suspected until intraoperative exploration or on final pathology [3, 28]. If during intraoperative exploration for parathyroid adenoma, invasion of adjacent structures is seen, the surgeon should consider en-bloc resection [6]. Frozen section pathology is unreliable for diagnosing parathyroid carcinoma due to the complexities outlined earlier. If the diagnosis is only made after the surgery then the final pathology including extensive vascular and capsule invasion, persistently elevated levels of PTH or imaging evidence of residual disease will guide whether reoperation may be beneficial [5, 28]. Localizing the residual disease with imaging will greatly increase the chances of success [27]. Nevertheless, these patients have a higher risk of recurrence than patients treated with primary en-bloc resection [27, 28].

Postoperative Care

Parathyroid hormone should fall precipitously after surgery, therefore, calcium levels should be monitored very closely in the immediate postoperative period as patients may develop "hungry bone syndrome," requiring high doses of PO or IV calcium and calcitriol [58]. Patients should also be monitored for concomitant hypomagnesemia as this can develop from increased bone uptake of magnesium and will exacerbate hypocalcemia by impairing parathyroid hormone release and action [58]. Patients treated preoperatively with bisphosphonates have some protection from hungry bone syndrome [59]. Even with only slightly decreased postoperative calcium levels some patients will develop paradoxical elevations in postoperative parathyroid hormone likely due to a combination of low vitamin D levels and bone remineralization [60].

Neurocognitive symptoms will usually rapidly improve postoperatively and in long-standing cases, the severity of these symptoms may now become fully appreciated. We have seen patients return to normal from what was felt to be fairly significant long-standing dementia following surgery.

At this time there is no evidence to support calcium supplementation to suppress residual parathyroid tissue; however, there is a case report of a patient responding to calcitriol supplementation [61]. When calcitriol was held on three different occasions, PTH rose substantially, therefore, calcitriol was continued indefinitely. This patient never showed anatomical evidence of recurrence with over 80 months of follow up.

Adjuvant Radiotherapy

Parathyroid carcinoma has traditionally been thought to be relatively radioresistant; however, several recent studies suggest decreased rates of recurrence with adjuvant radiotherapy [25, 26, 62]. We first published the Princess Margaret Hospital experience in 1998 for ten patients referred for consideration of radiation therapy between 1958 and 1996 [26]. Six of seven patients referred for adjuvant treatment where treated for positive microscopic margins and had no evidence of recurrence at an average follow up of 62.3 months. Two of three additional patients referred for palliative radiotherapy died of the disease.

In a larger overall series from MD Anderson, 6 of 18 patients with locally invasive disease were treated with adjuvant radiation therapy [25]. Only 1 of these patients developed recurrence compared to 10 of 20 patients who did not receive adjuvant radiation therapy. The experience from the Mayo clinic parallels this [62]. Four patients out of 61 were treated with adjuvant radiation

therapy due to concerns for microscopic residual disease. None of these patients showed signs of recurrence at an average of 60 months of follow up. Patients who received high dose radiation therapy for unresectable locoregional disease achieved locoregional control from 24 months up to 218 months.

This contrasts with a more recent study from our institution on 16 previously untreated patients [28]. All patients underwent surgical treatment and 11 (69 %) underwent adjuvant radiotherapy for high risk features and positive microscopic margins. This is the largest published series of patients receiving adjuvant radiotherapy. Seven patients (44 %) developed recurrence at a mean time of 61 months (2–143 months), all of whom had undergone adjuvant radiation. Most of these patients (86 %) had only undergone simple parathyroidectomy, while none of the patients who were initially treated with en-bloc resection recurred. This suggests that radiation therapy may have a role in high risk disease but cannot substitute for complete en-bloc surgical resection.

Chemotherapy

There is very limited experience with chemotherapy for parathyroid carcinoma. Most attempts to control metastatic disease with various agents have been unsuccessful. However, there are a few case reports using dacarbazine alone [63] or in combinations with 5-fluorouracil and cyclophosphamide [64] as well as a combination of methotrexate, adriamycin, cyclophosphamide, and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea [65] that appeared to slow progression of the disease. Unfortunately, the disease is so rare that it is difficult to adequately evaluate different chemotherapy agents and regimes.

Targeted Biologic Agents

There is new enthusiasm for potential activity of several biologic agents against the disease [6]. As previously discussed, a high percentage of patients with parathyroid carcinoma harbor a HRPT2 mutation leading to decreased production of parafibromin, which normally blocks cyclin D1. Cyclin D1 is thereby overexpressed in 91 % of parathyroid carcinomas and is an important regulator of cell cycle progression from G1 to S phase (Fig. 31.1) [6, 66]. This regulation occurs through modulation of the inhibitory activity of the retinoblastoma susceptibility protein (Rb), which is dependent on sequential phosphorylation events by cyclin dependant kinases 4 and 6 (CDK4 and CDK6) complexed with cyclin D1 [66]. Abnormalities in the cyclin D1-CDK4/6 pathway are not unique to parathyroid carcinoma and overexpression of cyclin D1 has been demonstrated in multiple human neoplasms in the head and neck, lung, bladder, pituitary, prostate, endometrium, and breast [66]. This has led to a major effort by multiple pharmaceutical companies over the last 20 years to develop CDK inhibitors and there are currently several agents in clinical trials for advanced solid organ tumors and lymphoma [66]. We are still awaiting the results of these clinical trials but hopefully this experience will translate to a therapeutic option for the much more rare and difficult to study parathyroid carcinoma.

Another new potential target is telomerase activity in parathyroid cancer cells. Telomerase has been demonstrated to be active in parathyroid cancers cells and not benign parathyroid lesions and can be used as a marker for malignancy [67]. Many human cancers exhibit upregulated or reactivated telomerase activity which helps them escape apoptosis. Azido-3′deoxythymidine (AZT) is a thymidine analog that is preferentially incorporated at the telomeric ends of chromosomes in cancer cells and can induce apoptosis. It has been shown to inhibit proliferation of human parathyroid cancer cell lines in vitro [68]. There are no reports of its use on patients but a clinical trial appears warranted.

Immunotherapy has been attempted in a patient with metastatic parathyroid carcinoma several years ago by immunizing her with tumor lysate and PTH pulsed dendritic cells [69]. Although an immune response was clearly demonstrated, it did not have any clinical effect on the patient.

Management of Recurrent and Metastatic Disease

Unfortunately recurrence rates are very high for parathyroid carcinoma with most series reporting a 40–60 % rate of locoregional recurrence [8, 25, 28]. In these series, most recurrences occurred between 2 and 5 years following initial surgery but some occurred even 10–20 years later. Metastasis most commonly occur in regional lymph nodes followed by lungs, bones, and liver [5]. Patients will generally present with gradually increasing PTH and calcium levels prior to any symptoms from mass effect [8]. The management approach is similar to primary treatment with first control of hypercalcemia, then localizing studies to identify the disease followed by surgical excision of resectable disease and possibly radiotherapy.

Control of hypercalcemia proceeds as outlined earlier in the chapter. The mainstay of management of long-term hypercalcemia are the bisphosphonates and cinacalcet.

Identification of the disease should include anatomic and functional imaging. Ultrasound of the neck is very helpful for assessment of nodal disease. CT of the neck, chest, and abdomen can identify local, regional, and distant metastases. This is further supplemented with a sestamibi scan to identify smaller metastasis. If these studies cannot identify the disease, selective venous catheterization and PTH measurement can be used in the neck [27].

Arguably, if the amount of disease is too small for identification by anatomic imaging, surgical exploration is unlikely to be successful. Surgical management of resectable disease, however, can provide very effective relief of symptoms and should be performed at locoregional and distant sites if possible [70]. Intra-operative radio-guided techniques may aid in difficult to localize tumors [71]. Wide margins should be attempted and all functioning tissue excised. This is justified even if it requires multiple operations as it provides excellent palliation that is not often achieved with medication alone [27]. Despite excellent palliation, surgical resection rarely results in cure and these patients will eventually succumb to complications of hypercalcemia rather than tumor burden [70]. The most common causes of death include renal failure, cardiac arrhythmias, and pancreatitis [70].

Surveillance

Due to the rarity of the disease, there are no prescribed guidelines on surveillance of parathyroid carcinoma. Postoperative PTH can give a sense of any residual disease and as outlined earlier, identifiable resectable disease should be removed surgically if possible even with multiple operations. PTH and calcium can then be monitored for recurrence and will rise prior to clinical symptoms from bulk of disease. Patients can recur many years after initial treatment and should likely be followed for life [25]. We recommend monitoring PTH and calcium every 3–6 months for the first 3 years, then yearly thereafter.

Prognosis

Parathyroid carcinoma is generally a slow but progressive disease. Overall recurrence rates range from 40 to 60 %. Five and ten year overall survival rates from a SEER study were reported as 92.5 and 66.8 % respectively [54]. An older NCDB study reported slightly worse 5 and 10 year overall survival rates of 85.5 and 49.1 % [4]. Median overall survival was 14.3 years in this study. Five and ten year disease specific survival rates were 100 and 80 % respectively from the most recent study from our institution [28]. Survival by stage is listed in Table 31.6 based on Talat's and Shulte's extensive review of the literature in 2010 [30].

Adverse prognostic factors vary considerably in the literature and include: lack of en-bloc resection at initial surgery, lymph node metastasis, distant metastasis, nonfunctioning tumors, vascular invasion on pathology, younger and older age, male gender, high number of recurrences, and high calcium levels at recurrence [9, 25, 27, 28, 30, 42, 54]. Of note, both the SEER and

NCDB studies did not demonstrate an association between tumor size and lymph node status on prognosis [4, 54].

Society Guidelines: N/A

Best Practices

1. Diagnosis:
   (a) Key to best outcomes is high level of suspicion preoperatively.
   (b) Patients will usually present with symptoms and complications of hypercalcemia, the most common of which are renal disease and bone disease. A third of patients will present with a neck mass.
   (c) A PTH ten times the upper limit of normal is strongly suspicious for carcinoma. Calcium may be mildly, moderately, or severely elevated.
   (d) Imaging should include functional imaging such as sestamibi-SPECT or PET and anatomic imaging such as US and CT or MRI.
   (e) Biopsy is not recommended.
   (f) Immunohistochemistry can considerably aid in making the pathologic diagnosis in equivocal cases.
   (g) Genetic testing for HRPT2 mutation should be strongly considered if available.
2. Preoperative preparation:
   (a) Correct hypercalcemia with IV fluid hydration, calcitonin, bisphosphonates, and cinacalcet.
   (b) Routine aggressive diuresis with loop diuretics is no longer recommended.
3. Surgical treatment:
   (a) Goal of surgery is en-bloc resection without violation of tumor capsule.
   (b) If during exploration for presumed parathyroid adenoma there is evidence for invasion of surrounding structures, consider en-bloc resection.
   (c) Lymphadenectomy is only performed if there is evidence of lymph node involvement (rare).
   (d) Resect distant metastasis if feasible.
4. Postoperative care:
   (a) Monitor for signs of hungry bone syndrome and replace calcium as necessary.
   (b) PTH should normalize. If it does not, perform workup for distant metastatic disease including anatomic imaging as well as sestamibi or PET. Resect distant metastasis if feasible.
5. Adjuvant treatment:
   (a) Radiation may be beneficial in patients with positive microscopic margins or other high risk features.
   (b) There is no evidence for the use of chemotherapy in the adjuvant setting.
6. Surveillance:
   (a) Monitor calcium and PTH for the first sign of recurrence.
7. Management of recurrence:
   (a) Resect distant metastasis if feasible.
   (b) In patients with widespread metastasis or unresectable disease, calcium can be controlled with bisphosphonates and cinacalcet.

Expert Opinion

Parathyroid carcinoma is a rare malignancy that often is diagnosed after surgical excision. One clue to the diagnosis before surgery is abnormally high PTH and calcium values at times to crisis level. Pathology is characterized by any one of malignant cellularity, capsular or vascular invasion. The workup of these patients, in addition to standard approaches to typical hyperparathyroidism should include (usually postoperative) cross sectional imaging and survey for distant disease. Genetic testing appears to hold promise for diagnosis and targeted treatment. Wide en bloc resection is the only primary treatment for this condition. Radiotherapy is administered for possible residual disease. Surveillance is comprised of clinical evaluation, biochemical testing, and imaging. Recurrences are managed by repeat surgery and/or external beam radiotherapy.

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Calciphylaxis

32

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Contents

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Historical Perspective

The term calciphylaxis was first coined in 1961 by Hans Selye who described a rat model for inducing acute cutaneous sclerosing lesions after systemic sensitization to calcifying factors such as vitamin D, parathyroid hormone, and sodium sulfathiazole [1]. In a series of experiments Selye exposed rats to systemic calcifying factors followed by subcutaneous challengers (albumin or metallic salt). The subsequent response was massive cutaneous calcification, inflammation, and sclerosis. He noted that the skin initially appeared painful but then developed into an exoskeleton-like skin in the area of challenge that was eventually shed to form new dermis [1]. Selye derived the term calciphylaxis from the series of events that appeared to be occurring—a systemic alteration of the body (phylactic response) to a challenging agent (calcifying agent) that resulted in morbid cutaneous lesions.

In 1969 a case report was published in the British Medical Journal that described a 21 year old man with end-stage renal disease who had been admitted for uremia and subsequently developed calcified cutaneous lesions. The authors drew parallels between the patient's symptoms with descriptions from Selye's rat model and described this finding as calciphylaxis presenting in man. The elevated calcium–phosphate levels and secondary hyperparathyroidism were thought

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to be the sensitizing agents. The patient had received subcutaneous iron-dextran, the challenging agent in the rat model, and subsequently developed anterior thigh plaques that appeared calcified on x ray and histology. The patient later died and no autopsy was performed [2].

Importantly there are differences between the calciphylaxis lesions described in the original rat model and those found in humans. In experimental models calciphylaxis was not limited to small and medium vessel calcification but rather produced a widespread subcutaneous response. This response produced an exoskeleton that could be shed, revealing new dermis that did not have the lesions, unlike the lesions found in humans [1]. Such differences have led to the proposed term calcific uremic arteriolopathy (CUA) to replace the term calciphylaxis, especially given the fact that calciphylaxis is indeed not a hypersensitivity reaction as previously believed [3]. As calciphylaxis has become increasingly recognized as a disease affecting both uremic and non-uremic patients some authors further argue that CUA is an inaccurate term and propose nomenclature that better encompasses the morphologic essence of calciphylaxis, such as obliterative calcific arteriopathy and microangiopathy [4, 5]. Other authors argue that calciphylaxis should be seen as a small artery-disease, distinguished from soft tissue calcification. However, calciphylaxis remains regarded as one of the subtypes of calcinosis cutis, a constellation of disorders in which calcium deposits form in the skin. Despite this the term calciphylaxis is still widely used in the medical literature, even to this day. Increasingly, calciphylaxis is seen as a multifactorial process that primarily involves vascular ossification-calcification and other associated damage to surrounding tissues and arterioles that lead to dermatologic, soft tissue, and visceral manifestations.

Pathophysiology

The exact pathophysiology of calciphylaxis remains poorly understood today. For many years it was thought that the final pathway to vascular calcification was by passive mineralization of calcium–phosphate deposits in subcutaneous arterioles, promoted by a state of hyperphosphatemia, hypercalcemia, and hyperparathyroidism (a process also known as "metastatic calcification"). However, advanced research in the molecular regulators of skeletal and extraskeletal mineralization has led to a more complex understanding of the pathway to human calciphylaxis. Vascular calcification is now thought to be mediated via a vast network of active cellular processes rather than by passive mineral deposition [6]. Further evidence suggests that the disease state of calciphylaxis results from a series of local and systemic insults that promote vascular and cutaneous injury. This more expansive analysis of the pathogenesis of calciphylaxis may better incorporate the puzzlingly varied clinical manifestations and heterogeneity of patients found to be diagnosed with the disease. Indeed, while a number of patients present classically with ESRD, hypercalcemia, and hyperparathyroidism ("uremic calciphylaxis"), another recognized subset of patients have normal kidney function, calcium, and PTH levels ("non-uremic calciphylaxis"). The latter group tends to present with known risk factors such as diabetes mellitus, obesity, and hypercoagulable conditions [3]. Furthermore, the presentation of calciphylaxis itself varies by the location of skin lesions (acral versus proximally located) and distribution through the body (cutis versus visceral calciphylaxis).

Despite the variants in clinical presentations, the diagnosis of calciphylaxis can be made by a combination of histopathologic findings and clinical presentation of the lesions. Biopsy specimens may show arteriolar medial calcification and subintimal fibroplasia, thrombotic occlusion of cutaneous vessels, ischemic necrosis of the subcutis, dermis, or epidermis and/or extravascular calcium deposition [6]. The pathway to calciphylaxis involves vascular stenosis and vascular thrombosis, two distinct and separate processes that are both required to produce clinical lesions of calciphylaxis [6]. This process of vascular calcification is thought to be mediated by the same intricate network of molecular and hormonal pathways that regulate osseous and extraosseous

mineralization. Imbalances in the system ultimately can lead to vascular smooth muscle cell (VSMC) differentiation to an osteoblastic phenotype which is thought to be ultimately regulated by activation of nuclear factor k-B (NFkB) [6, 7].

NFkB is an important transcription factor for many regulatory cellular functions. As it pertains to the osteogenic pathways, overactivity of NFkB is associated with mineral bone loss while inhibition of NFkB is associated with osteoporotic bone. The receptor activator of NFkB (RANK), its ligand (RANKL) and osteoprotegerin (OPG, a "dummy" antagonist of RANKL) are regulators of the production of transcription factor NFkB. Various medications, agents, and disease states are responsible for the upregulation or downregulation of these proteins that then ultimately affect the production of NFkB activity. It is thought that factors leading to a deficiency or inhibition of RANK and RANKL (bisphosphonates, recombinant OPG, anti-RANKL antibodies) can inhibit vascular calcification. Deficiency of OPG can lead to osteopenia and vascular calcification at an early age [6]. On a cellular level the process of vascular calcification is largely mediated by endogenous and exogenous agents that transform VSMCs in the arteriolar media to an osteogenic phenotype. Indeed, studies have shown that cultured VSMCs undergo calcification and adopt an osteogenic phenotype when subjected to high concentrations of calcium and phosphate in vitro [8, 9].

Other important mediators of vascular calcification include the extracellular matrix and fetuin-A, an inhibitor of vascular calcification and negative acute-phase reactant synthesized by the liver that is found to be downregulated in inflammatory states and in CKD patients. Recent focus has been on the ectopic production of osteopontin by smooth muscle cells in the vessel wall. Osteopontin is a phosphorylated matrix protein that is found in a variety of tissue and is synthesized by many cells types including fibroblasts, osteoblasts, osteocytes, odontoblasts, smooth muscle cells, and endothelium. It plays an important role in the pathogenesis of ectopic bone formation. Some studies have examined the role of osteopontin as a diagnostic marker for cases where calcium deposition is not obvious on histology. Magro and colleagues hypothesized that a combination of a pro-coagulant state in addition to certain risk factors and elevated osteopontin levels worked together to lead to calciphylaxis. Risk factors included being female, increased serum phosphate and alkaline phosphatase and lower levels of serum albumin [4].

Risk Factors

Several risk factors for calciphylaxis have been studied in case control series. Dysregulation of the calcium-phosphorus bone mineral axis in ESRD patients is among the most widely recognized. Elevated calcium-phosphorus product, hyperphosphatemia, hypercalcemia, and hyperparathyroidism are often present. However, low or even normal laboratory values can also be possible at the time of diagnosis. Calciphylaxis is more often seen in women at a 2:1 ratio to men, and more prevalent among Caucasian patients [3]. Trauma, diabetes mellitus, hypercoagulable states, and undernutrition are also risk factors [10]. Medications such as coumadin, corticosteroids, and iron therapy may also enhance vascular calcification [3].

Clinical Presentation

Epidemiology

Calciphylaxis is a rare disorder, estimated to occur in 1–4 % of patients with ESRD [11, 12]. One small population based study found the incidence to be 4.5 per one million people per year [13]. In 2009 a nationwide survey was performed in Japan querying over 1800 hemodialysis centers on their reported numbers of calciphylaxis. In over 10 years, 249 cases were reported at 151 centers. Seventy-two sporadic cases were also described in the Japanese literature, bringing the prevalence rate of calciphylaxis in Japan to less than three cases per 10,000 hemodialysis patients per year [14]. Interestingly, only

6.4 % of practitioners reported knowing what calciphylaxis was, while 60 % noted they did not. The incidence of non-uremic calciphylaxis diagnoses is even less certain, known only by the numerous isolated case reports of unusual presentations described in the literature.

Clinical Presentation

Patients with calciphylaxis typically present with exquisitely painful cutaneous lesions and violaceous mottling that resembles livedo reticularis. Over time these lesions can progress to ulcerations with overlying eschar that are further susceptible to secondary infection as they expand in size, depth, and number. The clinical presentation of cutaneous lesions is characterized by a biphasic process. In phase 1, the primary lesions are described as leathery areas of skin with induration and superimposed pruritic and painful erythematous nodules or plaques. These lesions tend to appear more in adipose tissue and can progress to deeper ulcerations. By phase 2 the lesions are similar to ischemic necrosis and have the appearance of nonhealing wounds with eschar and the potential for complications such as infection, abscess, and gangrene [15] Fig. 32.1.

Although the majority of case reports describe deep ulcerations as the hallmark finding on initial physical exam, this may in fact represent a delayed recognition of the disorder as early lesions can be easily mistaken for cellulitis or other dermatologic disorders. One Canadian series noted that the presenting symptom in 80 % of their patients was subcutaneous indurated plaques on their lower extremities. After identifying their first five patients with calciphylaxis, they prospectively studied and diagnosed a total of 36 patients over 7 years. Such heightened awareness of the disease likely led to recognition of lesions earlier in their evolution [16]. Although skin findings are the most common clinical presentation, other symptoms such as painful myopathy or rhabodmyolysis have been reported as the initial symptom, preceding the appearance of skin lesions [17].

The distribution of cutaneous lesions is described as being located either distal (extremities) or proximal (trunk/buttocks/face), with distal lesions appearing to have a better survival rate. Typically such lesions appear to occur in areas of high adipose content. Although skin lesions are the more classic presentation, visceral calciphylaxis has been described with rare case reports describing findings such as in cardiac,

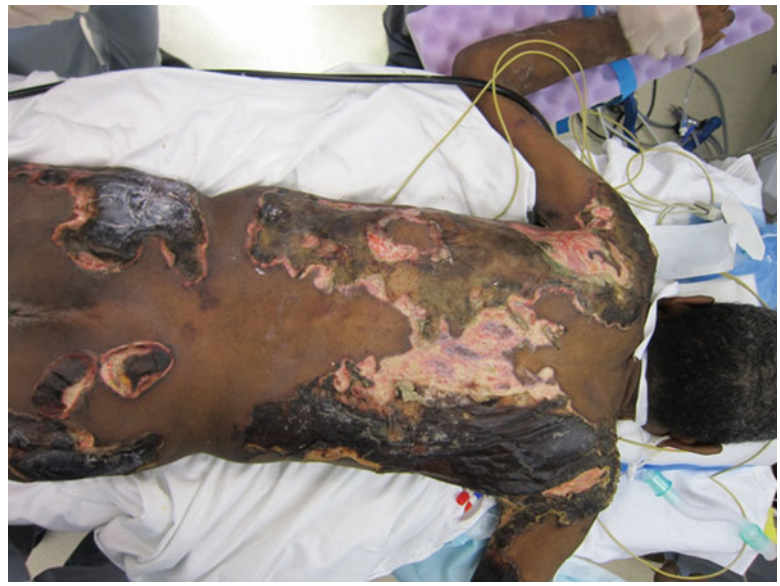

Fig. 32.1 Advanced calciphylaxis

pancreatic, and ocular locations [18–20]. In one case report, a patient with ESRD and rhinoorbitocerebral mucormycosis developed temporal artery calciphylaxis by biopsy and 2 weeks later presented with cutaneous extremity lesions [21]. Penile calciphylaxis is another rare but well described presentation, with over 30 cases reported in the literature over the previous decade, the majority of whom had ESRD and additional lesions in other sites besides the genitalia [22].

The differential diagnosis for calciphylaxis includes atherosclerotic vascular disease, cholesterol embolization, nephrogenic systemic fibrosis, oxalate vasculopathy, purpura fulminans, vasculitis, diabetic gangrene, and warfarin necrosis [3]. It may be difficult to determine the type of lesion as many other disease processes can mimic the appearance of ulcerating lesions, particularly ischemic necrosis and diabetic gangrene in the population of patients with ESRD from vascular or diabetic etiologies. A thorough history and physical exam, including evaluation for risk factors should be performed on patients presenting with clinical findings concerning for calciphylaxis.

Calciphylaxis is associated with high morbidity rates that are a consequence of severe pain, wound infections, recurrent hospitalizations, and multiple surgical interventions. Mortality rates are extremely high. The 1-year mortality has been reported between 45 and 80 %, with severe systemic infection and subsequent sepsis being the leading cause of death [3, 16, 23]. Patients with skin lesions that progress from subcutaneous to ulcerating lesions also appear to have higher mortality rates, up to 89 % described in one series [16].

Diagnosis

Laboratory Evaluation

There are no specific laboratory values that make the diagnosis of calciphylaxis. Patients can present with either uremia or normal renal function. Therefore selection of laboratory values to obtain should be based on the differential diagnosis and risk factors. Thorough investigation includes pursuing studies in the following systems: (1) renal function evaluation: serum urea nitrogen, creatinine, glomerular filtration rate; (2) mineral bone parameters: serum calcium, phosphorus, alkaline phosphorus, intact PTH, 25-hydroxyvitamin D; (3) liver evaluation: liver function panel including albumin; (4) infectious workup: complete blood count, blood cultures if indicated; (5) coagulation panel; (6) hypercoagulation panel: protein C, protein S, antithrombin III, antiphospholipid antibody; (7) evaluation for autoimmune or other inflammatory conditions or malignancies [3].

Radiographic Evaluation

Imaging with X-rays and nuclear bone scans has been reported in some case series as a tool to diagnose calciphylaxis [16]. Findings may show vascular and soft tissue calcification. However, there has not been systematic evidence describing the utility of imaging in the diagnosis or treatment of calciphylaxis. At this time there is no routine imaging that is recommended.

Histopathologic Evaluation

A definitive diagnosis of calciphylaxis can be made based on pathologic evaluation of the affected lesions combined with clinical examination and history. However, while the diagnostic advantages of performing a skin biopsy are clear, there are certain risks that must be considered. Importantly, biopsy of affected lesions can potentially propagate new lesions or lead to superinfection, bleeding, and worsening of already present ulcerations. If biopsy is necessary to rule out other potential diagnoses, it is critical that an experienced dermatologist or surgeon perform the procedure in order to maximize tissue yield and reduce the risk of requiring a repeat procedure. Generally a punch biopsy is preferred over incisional biopsy, with greatest diagnostic yield at the periphery of the ulcer rather than the base [3].

Histopathologic features of calciphylaxis can be considered based on location: (1) vasculature—vascular calcification of small and medium sized vessels, intimal hyperplasia, and intra-luminal thrombus; (2) extravascular—extravascular soft tissue calcification, septal and lobular panniculitis, dermal-epidermal separation, epidermal ulceration. By pathogenesis it is likely that arteriolar calcification is the primary event, with intimal proliferation and intravascular thrombosis being secondary and leading to ischemic necrosis and ulceration. Unfortunately histology alone cannot always provide a clear diagnosis as the differential diagnosis for medial calcification and panniculitis include atherosclerotic peripheral vascular disease, Mönckeberg sclerosis, warfarin skin necrosis, and other thrombotic disorders. Additionally, calcification of medium-sized vessels is a well-recognized histologic feature of patients with long-term renal failure on hemodialysis. Therefore it is important to use clinical history and exam in addition to histopathologic findings to aid in the diagnosis of calciphylaxis.

Specific diagnostic markers for calciphylaxis based on histology are forthcoming. Various histochemical stains can be employed for the detection of calciphylaxis. One study compared the usefulness of von Kossa versus Alizarin red staining and found that both types of stains appeared to be comparable although Alizarin red appeared larger and birefringent [12]. Perieccrine and pericapillary calcium deposits may also be features more specific to calciphylaxis [12, 24]. One study investigated the use of osteopontin expression as a potential diagnostic marker for calciphylaxis. Smooth muscle cells within the vessel wall may produce ectopic osteopontin as one of the early processes in the calcification that occurs during calciphylaxis, making such study of osteopontin interesting as a diagnostic marker. In a series of 25 biopsies from patients diagnosed with calciphylaxis, immunohistochemical staining for osteopontin was performed in addition to von Kossa staining. Osteopontin was predominantly located in subcutaneous fat and calcified vessels, although it was also found in vessels without calcification. Although there was no clear diagnostic utility, it is possible that higher levels of osteopontin in histologic staining can be suggestive of calciphylaxis and can help direct therapeutic interventions to reduce expression [4].

Treatment

The treatment for calciphylaxis requires a multidisciplinary approach. Contributions from the disciplines of nephrology, dermatology, pathology, infectious disease, pain management, nutrition, and surgery are key to optimizing management and determining the best interventions for each patient. Multiple treatment strategies have been described for calciphylaxis but unfortunately the quality of evidence remains poor and is limited to institutional experience, retrospective and cohort studies, case series, and case reports [25]. However, as the pathophysiology of calciphylaxis becomes better elucidated, physiology-directed treatment strategies and early diagnosis offer patients a better chance for improved outcomes [26]. Early therapy was once guided by wound management and supportive care for underlying sepsis. While these modalities are pillars in the treatment of calciphylaxis, further investigations in the medical management and reduction of risk factors are becoming prevalent. Today general treatment strategies focus on decreasing calcium and phosphate levels, controlling risk factors, pain control, aggressive wound management, and parathyroidectomy.

Wound Care Management

Routine surgical management is controversial for calciphylaxis and an attempt to minimize surgical debridement is encouraged. Some investigators argue that there may be an increased risk of furthering massive ulcerations in patients already predisposed to poor wound healing. Calciphylaxis lesions should therefore be approached according to the general principles of local wound care management. In order to facilitate healing, a wound bed must be free of devitalized tissue, biofilm, and exudate. As with all wounds, the need for surgical debridement must be made on a

case by case analysis by an experienced surgeon. Noninfected, superficial, dry wounds with eschar may not require surgical debridement, while clearly necrotic wounds with exudate and infected, nonviable tissue in patients with sepsis should undergo debridement for control of the infection and prevention of further tissue necrosis. Early defect closure in select patients may facilitate wound healing. One case series of seven calciphylaxis patients described managing ulcers with deep shaving of subcutaneous tissue down to fascia and immediate autologous split-skin grafting. The authors found a 30–90 % take rate of the grafts with complete healing of the ulcers in six of the seven patients [27].

Other adjunct therapies that have been described with variable success are vacuum-assisted closure of wounds, hyperbaric oxygen therapy, and sterile maggots [28]. One case report described using vacuum-assisted closure in two patients with calciphylaxis lesions affecting 10 and 48 % of the total body surface area. The latter patient died from fungal superinfection while the former patient survived [29]. Hyperbaric oxygen therapy has been used with some success in the treatment of nonhealing vascular wounds and necrotizing soft tissue infections. The therapy requires remaining in a sealed chamber and breathing 100 % O2 in order to restore tissue PO2 to higher levels and promote fibroblast proliferation and angiogenesis. This therapy, however, is limited by lack of access at many facilities and claustrophobia for patients. The use of sterile maggots in patients who were unable to tolerate routine local wound care has been described in sporadic case reports with success [30].

Parathyroidectomy

Parathyroidectomy has been used as a treatment for calciphylaxis in patients with ESRD and secondary hyperparathyroidism in an attempt to reduce PTH, calcium, and phosphate levels. Numerous small case series and reports have described improved wound healing and prolonged survival in patients who have received parathyroidectomy [31, 32]. Girotto and colleagues retrospectively reviewed outcomes of 13 calciphylaxis patients who had undergone either medical therapy ($n=7$) or parathyroidectomy ($n=6$). All six patients who received parathyroidectomy had significant reductions in PTH, calcium, and phosphate levels opposed to those who were treated medically. The median survival of those who underwent parathyroidectomy was also longer than those who did not (36 vs. 3 months, $P=0.021$) [33]. However, recent retrospective studies have not shown significant differences in outcomes between those who received parathyroidectomy and those who received only medical therapy [23, 34]. The lack of patients studied in both retrospective studies and case reports make it a major limitation in determining the efficacy of parathyroidectomy.

Sodium Thiosulfate

Sodium thiosulfate has been used for over 100 years as an antidote for cyanide poisoning and more recently for prevention of ototoxicity related to carboplatin treatment. In recent decades it has played a role in treating recurrent calcium urolithiasis and tumoral soft tissue calcifications in patients with ESRD [35]. It was first described as a successful treatment for calciphylaxis in a 2004 case report by Cicone and colleagues, with over 40 cases being subsequently reported in the literature [36–38]. Treatment with sodium thiosulfate typically results in rapid relief of pain and regression of skin lesions over the weeks following initiation of therapy. Although the exact mechanism of therapeutic action is unknown, it is hypothesized that the antioxidant effects and chelating property of sodium thiosulfate (thiosulfate binds with calcium, resulting in a highly soluble calcium thiosulfate salt) are the reasons for the improvement in symptoms. With no current randomized controlled trials available to validate the efficacy of therapy or the optimal dosing, route and duration of treatment, administration of treatment varies across reports. Sodium thiosulfate dosages range from 5 to 25 g intravenously, three times a week for up to several months [25, 38].

Bisphosphonates

Bisphosphonates are known inhibitors of osteoclasts and are used in various disorders (osteoporosis, Paget's disease, and hypercalcemia of malignancy) to help prevent loss of bone mass. In recent years several case reports have described successful treatment of calciphylaxis using bisphosphonates, with rapid pain relief and wound healing within months [39–41]. The mechanism of action is believed to be due to inhibition of macrophages and suppression of inflammatory cytokine release [42]. Adverse reactions to bisphophonates include hypocalcemia, hypophosphatemia, fever, osteonecrosis of the jaw, and should be used cautiously in patients with chronic renal failure with glomerular filtration rate of less than 30 ml/min. However, the use of bisphophonates in patients on hemodialysis may be mitigated by their ability to be dialyzed. There are currently no randomized trials investigating the use of bisphosphonates for calciphylaxis, and such therapy should be used on a case by case basis.

Cinacalet

Cinacalcet is a calcimemtic agent that is used for treatment of secondary hyperparathyroidism in patients with chronic kidney disease and in patients with parathyroid cancer and hypercalcemia [25]. Cinacalcet functions by increasing the sensitivity of calcium-sensing receptors on parathyroid cells to calcium, thereby leading to PTH suppression. The use of cinacalet in calciphylaxis has been described in a limited number of case reports [43, 44]. Authors reported pain relief in weeks to months and ulcer resolution in up to 14 months. The use of cinacelet was used primarily to control elevated calcium, phosphate, and PTH levels and is of uncertain utility in patients without elevated PTH levels. Treatment doses have been described as between 60 and 120 mg daily until resolution of symptoms. The use of cinacalcet in reducing the incidence of calciphylaxis in patients with ESRD has recently been investigated in a randomized controlled trial (EVOLVE trial). Over 3800 patients on dialysis were randomized to receive cinacalcet or placebo and followed up for 4 years. Of the 24 patients who developed calciphylaxis, 18 had been assigned to placebo and six had received cinacalet ($P=0.014$), suggesting that cinacalcet may reduce the incidence of calciphylaxis in patients with ESRD [45].

Conclusion

Calciphylaxis is a rare disorder characterized histologically by medium vessel calcification and clinically by painful, ulcerating skin lesions. Although described predominantly among patients with end-stage renal disease, patients with normal kidney function may also be affected. Outcomes of calciphylaxis remain poor to this day, with significant morbidity and mortality arising from septic complications of infected wounds. Future studies investigating the pathophysiology and identifying important multifactorial risk factors may lead to earlier recognition and treatment of calciphylaxis.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion
Calciphylaxis is usually seen in dialysis patients and generally indicates a near term mortality, usually due to wound related sepsis. The diagnosis is not always obvious and biopsy can be problematic due to poor wound healing which can then lead to sepsis and death. Therefore, parathyroidectomy should be performed early for a chance to alter the course of the disease. Additional research is warranted to delineate the diagnosis and treatment of this rare disease.

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Clinical Genetics and Heritable Parathyroid Disease: Monogenic Disorders

33

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Contents

Introduction

The ever-increasing speed of data processing has led to more precise and less expensive genome analysis [1]. Genome-wide arrays and next-generation sequencing are increasing our ability to determine the genetic contribution to disease [2]. Despite these advances, the precise cause for the majority of genetic contribution to common disease (hypertension, diabetes, and most cancer) continues to be unexplained [3]. Monogenic disorders are an exception and are therefore the main focus of this chapter.

While a strictly monogenic disorder is rare for any given person in the general population, over 4000 such disorders exist and so the aggregate impact is significant. When a single mutated gene causes a disease process there are often large and lasting consequences for the patient and family. The disorders discussed in this chapter may impact only a small proportion of patients but are highly important to recognize because they may aid in drug discovery [4], provide insight into unsuspected biological mechanisms [5] and determine treatment with implications for generations of other family members.

Clinical genetic tests can be used to identify abnormalities at the chromosome level or at the single-gene level. Cytogenetic tests can identify genetic alterations such as deletions and duplications at the chromosome level, and include

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karyotype and fluorescent in situ hybridization (FISH). Chromosomal microarray (CMA) is used to identify microdeletions or microduplications that would not be identified on standard chromosome analysis. These tests can be useful in the diagnosis of multiple conditions such as 22q11 deletion (Velocardiofacial/DiGeoge Syndrome), in which there are multisystem manifestations.

The interpretation of these tests is often challenging, as microdeletions or microduplications without clinical consequence, known as benign copy number variants, and variants of uncertain significance are frequently identified [6]. CMAs can be performed using several different platforms, including bacterial artificial chromosomes, oligonucleotide probes ("oligoarrays"), and more recently single nucleotide polymorphism (SNP) arrays. SNP arrays can identify areas of the genome where there is loss of heterozygosity—that is, areas where both copies of the chromosome are identical.

Molecular tests identify genetic alterations at the level of a gene. These include sequencing, methylation, repeat number, and deletion/duplication tests. Traditionally (over the past 10 years), a gene-by-gene approach was used for molecular testing where the most likely gene based on clinical presentation was tested first, then proceeding with sequencing other genes if diagnosis remained uncertain. However, recent implementation of next-generation sequencing has led to the use of multigene panels. This means that multiple genes implicated in a clinical process may be tested all at once. While there are advantages of casting a wider net, panels should be ordered and interpreted with caution as inclusion of specific genes in a panel varies widely and is highly laboratory specific, and testing a larger number of genes increases the chance of finding a variant of uncertain significance. To further increase complexity, gene panels will likely be replaced by whole exome and whole genome sequencing. Interpretation is and will continue to be an area of active debate and change in genetic medicine [7].

In summary, germline genetic tests (whether at the chromosome or molecular level) are extremely helpful for clinical diagnosis when a known mutation is found, but there are many reasons why testing and interpretation is not straightforward. Polymorphisms of uncertain significance and rare variants with questionable effect on protein function are often identified in genetic tests, and the classification of these variants is an ongoing process [8]. Due to these complexities as well as ethical, legal, and social issues inherent in all genetic testing, genetics consultation should be offered and available in clinical scenarios where genetic testing is considered.

The following sections pertain to the monogenic disorders in which the genetic contribution to hyperparathyroidism is well established, but be advised as this is a time of rapid change and this list will likely expand over the next few years.

Familial Hypocalciuric Hypercalcemia

Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant cause of hypercalcemia, caused by heterozygous mutations in one of three genes: *CASR* (calcium-sensing receptor) [9], *GNA11* (guanine nucleotide-binding protein, alpha-11) [10] and *AP2S1* (adaptor-related protein complex 2, sigma-1 subunit) [11]. The vast majority of cases are due to inactivating mutations of *CASR*. Additionally, individuals with homozygous mutations in *CASR* can present with neonatal severe primary hyperparathyroidism [9]; this will be discussed further in the next section.

CASR encodes the calcium-sensing receptor expressed in parathyroid cells, osteoblasts, osteoclasts, bone marrow, kidneys, and others [12]. In the parathyroid gland, activation of the receptor by the presence of ionized calcium leads to decreased production of PTH. In the kidney, activation of the receptor leads to decreased reabsorption of calcium and magnesium, and decreased urine concentrating ability. Therefore, mutations resulting in decreased function of the receptor have two main effects: continued activation of PTH release and excess reabsorption of calcium despite normocalcemia. The end result is hypercalcemia with hypocalciuria [13].

GNA11, the second gene in which inactivating mutations were discovered as causative of FHH, encodes a guanine-binding second messenger for the calcium-sensing receptor. Normally, agonism of the receptor results in activation of phospholipase C which is one of the mechanisms that inhibits PTH release from the parathyroid cells [10]. *AP2S1* mutations can also lead to FHH; the mutated gene appears to affect the endocytosis of calcium-sensing receptors [11].

Regardless of the gene, the resulting hypercalcemia is usually benign, as heterozygotes still have one functioning copy of the affected gene, and about 50 % of their receptors are expected to work normally. The diagnosis is usually made incidentally during childhood. A mild, persistent, asymptomatic hypercalcemia is characteristic [14]. PTH levels are usually normal, but may be high in 20 % of cases [13]. Other findings are hypocalciuria and hypermagnesemia. Exceptionally, FHH can be severe and present with chondrocalcinosis and pancreatitis, but the usual symptoms of hypercalcemia are absent.

When present, hypocalciuria is an important feature to help distinguish FHH from primary hyperparathyroidism. There are two methods of quantifying calcium excretion: in 24 h urine collection, the total calcium excretion is lower than 200 mg/day [14]. Another method is the calcium to creatinine clearance ratio, which is easier to collect. Patients with FHH usually have a value of <0.01. Values above 0.02 are characteristic of primary hyperparathyroidism [15].

The overlap in calcium excretion between FHH and primary hyperparathyroidism presents a clinical challenge for diagnosis and highlights the importance of genetic testing. Atypical cases with hypercalciuria in the presence of a CASR mutation have been identified. Making the correct diagnosis is important because patients can avoid parathyroidectomy in most cases of FHH [16]. Some of these patients may present with nephrolithiasis or pancreatitis—in these exceptional instances, partial parathyroidectomy can be beneficial [17].

When clinical suspicion is high, genetic testing is the most conclusive way to diagnose FHH [16], but current gene testing cannot rule out the disease (high specificity, low sensitivity). This is because about one-third of families have mutations in either other genes or other areas (possibly distant regulatory sequences) controlling gene expression and these mutations are missed by current sequencing techniques [12]. Also, FHH has autosomal dominant inheritance, but incomplete penetrance or de novo mutations could result in an affected patient whose parents have normal calcium levels giving the appearance of "skipped" generations. This may lead to under diagnosis of disease in a family with significant consequences. False negative tests may occur due to differences in laboratory panels, sequencing read depth, and subsequent reporting differences.

Neonatal Severe Hyperparathyroidism

Neonatal severe hyperparathyroidism (NSHPT) results from homozygosity or compound heterozygosity for inactivating mutations in *CASR* [9]. Therefore it usually presents with autosomal recessive inheritance. Patients present in infancy with hyperparathyroidism, with very high PTH levels that are several times the upper limit of normal. The resulting hypercalcemia is severe, with calcium levels greater than 15 mg/dl with inappropriately low urinary calcium excretion. Infants can have severe bone demineralization leading to multiple fractures and failure to thrive [18]. The only definitive intervention is emergent parathyroidectomy; otherwise, the disease is fatal [12]. Pamidronate and calcitriol can be used pre and postoperatively to aid in the management of the calcium levels [19].

In some cases, a heterozygous dominant-negative mutation in *CASR* can cause neonatal hyperparathyroidism [20]. In this scenario, the missense mutation reduces both the function of the gene product from the mutated allele, and interferes with the gene product from the normal allele. In these cases, the inheritance is autosomal dominant, but both alleles are functionally affected. These patients tend to have a relatively milder course than NSHPT and can be treated pharmacologically, with careful monitoring similar to FHH [12].

Hyperparathyroidism-Jaw Tumor Syndrome and *CDC73*-Related Parathyroid Carcinoma

Hyperparathyroidism-Jaw Tumor Syndrome (HPT-JT) is an autosomal dominant disease caused by heterozygous loss-of-function germline mutations in the *CDC73* gene (Homolog of S. cerevisiae cell division cycle protein 73) [21]. The gene product is parafibromin, a subunit of the PAF1 protein complex. The complex localizes in the nucleus and is thought to be a transcription factor [22]. Somatic mutations in *CDC73* are frequently found in parathyroid carcinomas, and transformation of parathyroid adenomas into carcinomas in HPT-JT patients occurs due to a "second hit" mutation in the wild type allele, proving that *CDC73* is a tumor suppressor gene [23].

HPT-JT presents as a complex of primary hyperparathyroidism, seen in up to 95% of individuals, usually caused by a single parathyroid adenoma;, cemento-ossifying fibromas of the mandible, present in 30–40% of patients; renal cysts in 20% of patients; frequent uterine tumors (multiple types); and infrequent manifestations such as renal hamartomas and Wilms tumors [24].

The primary hyperparathyroidism can present as early as 7 years of age [25], but the usual range of presentation is late teens to early 20s [26]. The causative parathyroid adenoma usually has cystic features [27]. In some cases, a synchronous or metachronous second adenoma may present, probably due to the tumor suppressor gene function of *CDC73*. Patients can also present with parathyroid adenocarcinoma, and nonfunctioning carcinomas have been reported [24]. Patients present the usual manifestations of hypercalcemia, such as fatigue, constipation, muscle weakness, and nephrolithiasis. The preferred treatment is surgical removal of the affected parathyroid gland followed by close monitoring of PTH and calcium for recurrence.

The cemento-ossifying fibromas can present either as an enlarging mass or as an incidental finding on dental x-ray. The tumors tend to enlarge, and can invade adjacent structures, potentially impeding breathing, interfering with dentition, and causing severe cosmetic deformity. Therefore, surgical management is often indicated [23]. The tumors usually arise in the molar and pre-molar areas and present before age 20. However, there are so-called "sporadic" tumors with a distinct histological appearance that can arise in other areas of the jaw, and present later in life.

The renal manifestations of HPT-JT include renal cysts, hamartomas, and Wilms tumor. The renal cysts can range from just a few to overt polycystic kidney disease resulting in end-stage renal disease [28]. The hamartomas are not thought to exhibit malignant transformation. Three families with HPT-JT have presented with Wilms tumor [24]. Uterine tumors include extensive adenomyosis, adenofibromas, leiomyomas, and occasional sarcomas [29]. Sporadic case reports of other tumors in HPT-JT syndrome include germinal cell tumors, neurofibroma, papillary thyroid carcinoma, and pancreatic adenocarcinoma [23]. It has not been conclusively established if these tumors are part of the syndrome or coincidental findings in the reported individuals.

Parathyroid carcinoma can be the only manifestation of a mutation in *CDC73*. These neoplasms are characterized by an extreme elevation of both calcium and PTH levels, profound symptoms of hypercalcemia such as muscle weakness, nausea, vomiting, pathological fractures, and altered mental status. The mass effect can lead to dysarthria and dysphagia. *En bloc* resection is the preferred method for the management of parathyroid carcinoma [24]. Genetic testing for germline mutations in *CDC73* should be considered in all patients with parathyroid carcinoma [30].

Multiple Endocrine Neoplasia Types 1 and 4

Hyperparathyroidism is the most common presenting sign in Multiple Endocrine Neoplasia, Type 1 (MEN1) and the newly described Multiple Endocrine Neoplasia 4 (MEN4). MEN1 is characterized by the manifestation of two or more characteristic endocrine tumors in the same individual and requires a high index of suspicion to diagnose

due to the myriad of possible presentations. At least 20 neuroendocrine and non-endocrine tumors occur in this syndrome. The most frequent tumors are the so-called "P triad"—parathyroid, pituitary, and pancreas neuroendocrine—tumors. Other less frequent tumors include gastrointestinal tract, adrenal cortex tumors, pheochromocytomas, and carcinoid [31]. Typical non-endocrine tumors are facial angiofibromas, collagenomas, lipomas, and ependymomas.

MEN1 is caused by heterozygous mutations in *MEN1*, a gene that encodes for menin [32]. Mutations in *MEN1* can also present as familial isolated hyperparathyroidism. Menin is not similar to any other mammalian protein [31]. Its role has been extensively studied, and its main effect appears to be control of gene expression [33]. The protein contains three nucleus-localization signals but there is no known genotype-phenotype correlation. It has been shown to regulate the histone methylation of CDK inhibitor genes [34]. Other effects of menin include interaction with p53, a key checkpoint in the regulation of DNA-decay mediated apoptosis, which may explain its role as a tumor suppressor gene [35]. Menin also has been implicated in the regulation of hematopoiesis by interacting with the MLL protein, and in the differentiation of osteoblasts [36]. MEN type 4 is a rare disease that appears to be clinically undistinguishable from MEN1 caused by mutations in a CDK inhibitor gene, *CDKN1B* [37]. By convention the term "MEN1" is reserved for the diseases caused by mutations in *MEN1* (the gene that encodes menin). Both *MEN1* and *MEN4* should be considered for testing when there is clinical suspicion of MEN1.

The parathyroid tumors usually present as mild primary hyperparathyroidism, often detected as a result of routine serum calcium measurement. The onset of hyperparathyroidism appears to be in the early 20s, and is slowly progressive and often asymptomatic. It is the initial presentation in 90 % of individuals with MEN1 [31]. Usually, the underlying disease affects multiple parathyroid glands and in the authors' opinion, MEN1 should be considered in a patient with hyperparathyroidism in their 20s to 30s especially in the setting of multigland disease. A discrete adenoma is rarely identified and optimal management is controversial. Therapies include selective parathyroidectomy of the affected glands, subtotal parathyroidectomy in which 7/8 of the parathyroid tissue is removed, and total parathyroidectomy with or without autologous transplantation to the forearm [38]. The risk of persistent hypocalcemia could be as high as 25 % after total parathyroidectomy, and the recurrence risk from subtotal parathyroidectomy could be as high as 50 % [31]. However, different studies report various rates of success from these surgical approaches.

Pituitary tumors are the next most common manifestation of MEN1 [31]. The most frequent type of adenoma is prolactinoma. The tumors tend to be larger than those seen in non-MEN1 patients. The tumors are usually solitary [39]. The tumors may produce more than one type of pituitary hormone, and symptoms are dependent on the hormone produced. Prolactinomas may present with galactorrhea or amenorrhea in women, and decreased libido or sexual dysfunction in men. These can be medically managed with dopamine antagonists [40]. Growth-hormone secreting tumors can present with gigantism or acromegaly. Transphenoidal surgery is the preferred therapy [31], with somatostatin analogs as a medical alternative [41]. ACTH-secreting tumors can lead to Cushing syndrome, neurosurgery (with occasional need for radiotherapy) is indicated [31, 41]. FSH-secreting tumors have been reported and require surgical management [42]. Nonsecreting pituitary tumors are also possible, and usually require surgery if symptomatic.

Gastrinomas are the most frequent neuroendocrine tumors in MEN1, present in 40 % of individuals. The tumors may present with peptic ulcers (Zollinger-Ellison syndrome), obstruction of the gastric outlet, or chronic diarrhea. Gastrinomas are frequently found in the first or second portion of the duodenum, are usually subcentimeter in diameter and 50 % have metastasized by the time of diagnosis [31]. The most frequent sites of metastasis are the liver and lymph nodes but primary lymph node gastrinomas have been reported [43]. Symptoms from

excessive gastrin production can often be managed with proton pump inhibitors or H2-blockers [44] but surgical removal may be a treatment option for patients with a discrete, large tumor.

Management of pancreatic tumors present unique challenges and treatment approach is highly patient dependent. These include insulinomas, glucagonomas, and VIPomas [31]. They typically present with symptoms corresponding to the respective hormone: hypoglycemia in the case of insulinomas, hyperglycemia with diarrhea, anemia, and necrolytic migratory erythema in glucagonomas, and the watery diarrhea, hypokalemia, and achlorhydria syndrome in VIPomas.

Other tumors seen in MEN1 include adrenocortical tumors, which are typically nonsecreting, carcinoid tumors (rarely associated with the carcinoid syndrome) and non-endocrine tumors. Skin findings include facial angiofibromas and collagenomas, which together can be seen in more than 80 % of patients and may serve as a clinical clue [45]. In less than 10 % of patients, meningiomas, ependymomas, and leiomyomas may be seen [31].

There is currently a lack of evidence from controlled clinical trials and the choice of biochemical and imaging screening will depend on resources, clinical judgment, and patient preferences. However, expert guidelines do exist. The International Guidelines for Diagnosis and Therapy of MEN Type 1 and Type 2 recommend the following surveillance for individuals diagnosed with MEN1: annual measurement of prolactin beginning at age 5, fasting serum calcium concentrations beginning at age 8, chromogranin-A, glucagon, fasting glucose and insulin, pancreatic polypeptide and vasoactive intestinal peptide annually beginning at age 8,fasting serum gastrin concentration starting at age 20, head MRI every 3–5 years starting at age 5, and abdominal CT or MRI every 3–5 years staring at age 20 [38].

Genetic testing for mutations in the genes causative of MEN 1 and 4 can be used to establish the diagnosis definitively in patients with more than one endocrine tumor and/or hyperparathyroidism. The single occurrence of a rare tumor such as an FSH-secreting adenoma should also raise the suspicion for MEN1 [31]. In the presence of a family history of hyperparathyroidism, patients with a history of severe reflux, unexplained hypoglycemia, hyperglycemia, or diarrhea should also be considered for testing. Whenever possible, it is best to start testing with a relative that has a clearly established diagnosis of MEN. A multiple gene panel including *MEN1, RET, CDKN1B*, and other genes potentially in the differential diagnosis (for example those causative of Hereditary Paraganglioma/Pheochromocytoma) is often the most efficient approach in patients without a family history. If a causative mutation is identified, first degree relatives can be tested for the known familial mutation and start surveillance for endocrine tumors pre-symptomatically. As with all genetic testing, the test results may be inconclusive or falsely negative and should be interpreted with caution.

Multiple Endocrine Neoplasia Type 2

Multiple Endocrine Neoplasia, Type 2 (MEN2) is an autosomal dominant condition caused by heterozygous mutations in the *RET* gene [46]. There are two recognized subtypes: MEN2A and MEN2B (5 % of cases [47]). MEN2 may present with parathyroid hyperplasia but the most prescient reason to diagnose MEN2 is to prevent medullary thyroid cancer in the patient and family. MEN2A can present with pheochromocytoma, parathyroid hyperplasia or adenoma, and medullary thyroid cancer (MTC). Familial medullary thyroid cancer (FMTC) is considered part of the spectrum of MEN2A, in which MTC is the only manifestation of the disease [48]. In MEN2B, patients have a distinct phenotype, with marfanoid habitus, prominent and full appearing lips and tongue due to the progressive development of neuromas (see Fig. 33.1 demonstrating the appearance of smooth palpable nodules on the lips and tongue and Fig. 33.2 (neuroma of upper lid margin)), and diffuse ganglioneuromatosis of the GI tract [49]. Patients who present with this appearance should be promptly evaluated for mutations in *RET* with subsequent management of MEN and surgical referral.

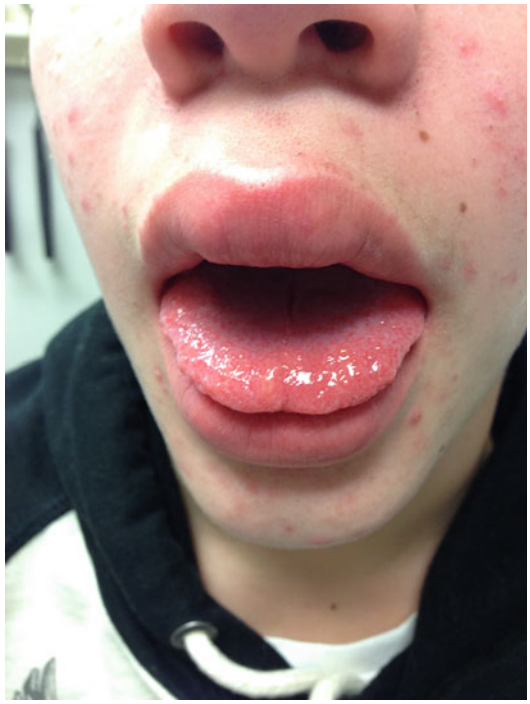

Fig. 33.1 Distinctive appearance of smooth palpable nodules on the lips and tongue in MEN2B

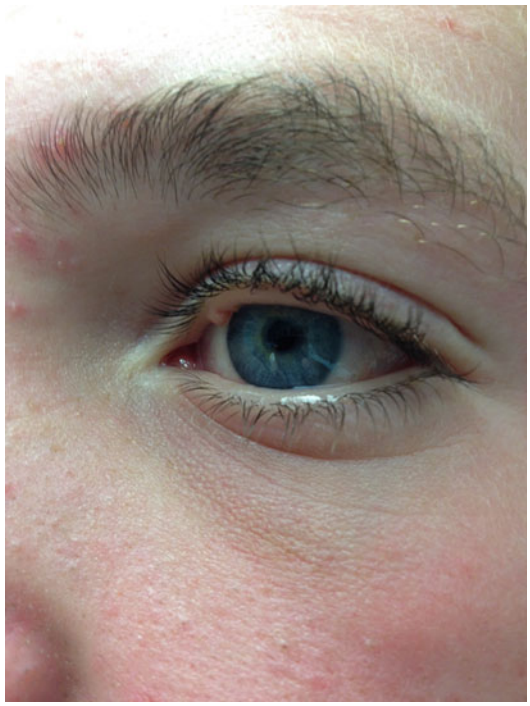

Fig. 33.2 Neuroma of upper lid margin in MEN2B

The *RET* gene (Rearranged during transfection proto-oncogene) encodes for a receptor tyrosine kinase known as RET, that interacts with the glial-derived neurotropic factor (GDNF) family of ligands and activates the MAP kinase pathway [50]. Unlike most inherited cancer syndromes, the mutations in the RET gene do not correspond to the two-hit hypothesis (in which the germline mutation is considered a first "hit" that must be followed by a somatic "hit" in the other allele), rather the mutations are gain-of-function [51]. This leads to a high penetrance (as much as 90 %), and early manifestations of disease [47]. Also, there are strong genotype-phenotype correlations, with certain mutations, especially p.Met918Thr, known to cause the MEN2B subtype [52]. Mutations have been classified into four risk levels, allowing for a more tailored management [49].

The first manifestation of MEN2A is usually MTC. It occurs in greater than 90 % of patients [49]. C-cell hyperplasia can predate the development of the MTC, as seen in specimens of patients who underwent prophylactic surgery [53]. The tumors are aggressive and 70 % of patients have regional node metastasis at the time of diagnosis [54]. The treatment is thyroidectomy with lymph node dissection [49]. Prophylactic thyroidectomy is indicated in patients diagnosed by genetic testing for mutations in *RET*. In general, the recommendation is for surgery before age 5, except in patients with low risk mutations and who have a family history of less aggressive MTC—these patients can be followed with annual calcitonin measurements and neck ultrasounds [48]. The penetrance of MTC in MEN2B is nearly 100 %. At the time of a new presentation, most patients have metastatic disease [47]. Therefore, if a patient has a high risk mutation associated with MEN2B (whether they have the full phenotype) prophylactic thyroidectomy is indicated at the earliest possible age [48]. After obtaining family history and subsequent definitive genetic testing, multiple family members may be offered prophylactic surgery and spared the significant morbidity and mortality of MEN2.

Pheochromocytomas are also seen in most patients with MEN2A and in 50 % of those with MEN2B [49]. About 4 % become malignant [55].

Unilateral (rather than bilateral) adrenalectomy has become the standard of care [48]. Screening for this manifestation should start at age 8 [49]. Hyperparathyroidism is usually subclinical or mild and typically presents many years after MTC [56]. As with hyperparathyroidism secondary to MEN1, there is no consensus on the optimal surgical management (partial, subtotal, or total parathyroidectomy with or without forearm autograft).

Because of the clear genotype/phenotype correlation, all patients with suspected MEN2 should have genetic testing and all patients with medullary thyroid cancer are candidates for testing regardless of family history. Patients with a pheochromocytoma presenting in childhood, and patients with a pheochromocytoma or parathyroid adenoma and a family history of endocrine tumors should also be considered for genetic testing. If the presentation is a pheochromocytoma, the differential includes the several genes causative of Hereditary Pheochromoctypma/Paraganglioma syndrome. MEN1 and 4 are also potentially in the differential diagnosis. As noted previously, these genetic test results should be interpreted with caution and may be inconclusive.

Summary

Most parathyroid disease at the present is felt to be spontaneous in nature. Several special patters of disease which include hyperparathyroidism may be hereditary. Specific patterns of hyperparathyroidism with thyroid cancer and other conditions should be appreciated the clinician and those patients should be sent for genetic consultation when appropriate. Cases of pediatric or young adult presentation of hyperparathyroidism and concerns for Familial Hypocalcuric Hypercalcemia should also be referred to a clinical geneticist. Geneticist referral may result in the identification for other kindred members which may suffer from hyperparathyroidism or other maladies

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion

A differential diagnosis for genetic causes of hyperparathyroidism must always be kept in the back of the clinician's mind. Common genetic conditions to be remembered include: Familial Hypocalcuric Hypercalcemia, Hyperparathyroidism Jaw Tumor Syndrome, and the multiple endocrine neoplasias.

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Parathyroid Cryopreservation and Autotransplantation

34

Marcelo F. Figari

Contents

Introduction

The possibility of preserving parathyroid cells is the basis for the current treatment of postoperative hypoparathyroidism. Until present results have been limited, however, the method may offer encouraging opportunities for parathyroid transplantation in all its modalities.

Throughout this chapter, we shall analyze the various situations that may eventually result in hypoparathyroidism and how preservation of parathyroid cells has evolved. Also, we will define recommendations for the current cryopreservation technique based on the best available evidence, assess the possibility of studying "in vitro" the potential for auto or allotransplantation, describe the evolution of immediate and deferred autotransplantation techniques, review current results, and, finally comment on the opinions available regarding cost-effectiveness of cryopreservation for institutions.

Indications for Parathyroid Cryopreservation

Hypoparathyroidism occurs due to resection or a vascular insult of the parathyroid glands during thyroid or parathyroid surgery. Although its incidence is low, long-term medical management is

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very difficult, given the lack of an established hormone replacement therapy [1]. Although parathyroid hormone has recently been a approved to treat hypoparathyroidism and may ameliorate sysmtoms.

In addition to the immediate metabolic disorders caused by the lack of parathyroid hormone, when the disorder is permanent it entails serious systemic consequences, such as osteoporosis due to the lack of osteocytic activity, and also cardiovascular, ophthalmic, and neurological disorders [2, 3].

The current indication for cryopreservation of parathyroid tissue includes all surgical settings where the possibility of postoperative hypoparathyroidism is foreseen. Hence, most dangerous situations are reoperations for persistent or recurrent hyperparathyroidism, and secondly, total or subtotal resection of the parathyroid glands performed to resolve sporadic or familial forms of primary, secondary, or tertiary hyperparathyroidism [4].

In cases of initial operations for hyperparathyroidism, several authors have suggested the use of intraoperative measuring of parathormone (PTH) as a sign of potential occurrence of hypoparathyroidism. When during surgery circulating PTH drops more than 80 %, they propose cryopreserving parathyroid tissue [2]. To the mentioned indications, we may add the need to perform a central neck dissection because of thyroid cancer, as well as reoperations for thyroid cancer, in cases in which the surgeon is not confident about the presence or vitality of the remaining parathyroid glands and considers it best to cryopreserve than to autoimplant parathyroid tissue, due to the potential for future interventions [2]. Hence, having cryopreserved tissue allows the surgeon to assess the patient's metabolic response after the initial surgical procedure, and postpone autotransplantation until a later, more convenient time.

Cryopreservation, together with the clinical applications mentioned, plays an essential role in the research area, since it provides tissue samples of various characteristics and obtained at different times, thus allowing investigators to perform experimental research [4].

However, cryopreserving parathyroid cells implies a latent risk, which is the higher failure rate of autotransplantation compared to when it is performed at the time of the initial surgery. Fresh autotransplantation is estimated to have, in average, an 80 % success rate, in contrast with about a 50 % success rate for cryopreserved transplanted tissue, with reports ranging from 17 to 83 % [4, 5].

Current Technique of Parathyroid Cryopreservation

First we should mention that preservation involves fragments, not isolated cells, since that improves the implant's functionality [4].

After extracting the parathyroid tissue and deciding how much tissue will be cryopreserved, the surgeon, preferably under magnification, eliminates the excess fatty tissue and selects those fragments with less nodularity (Fig. 34.1). At that time, or later in the laboratory, the tissue to be cryopreserved should be cut into fragments of 1–2 mm^3 [2, 4, 6] (Fig. 34.2). From the operating room, the parathyroid tissue removed is transported at 4 °C in a Dulbecco's modified Eagle medium (D-MEM, Gibco®) (Fig. 34.3), generally supplemented with antibiotics (for example 100 U/ml of penicillin, 100 μg/ml of streptomycin and 0.25 μg/ml of amphotericin). Together with the sample placed in the transport medium, a patient's blood sample is sent, to obtain the plasma that will be included in the final cryopreservation process [7, 8].

In most institutions, the final preservation medium used is the Roswell Park Memorial Institute solution (RPMI) 1640, at concentrations ranging between 60 and 80 %, with the addition of 2 mM of glutamine and 5 μg/ml of penicillin streptomycin or 50 μg/ml of gentamicin [9]. Between 40 and 60 particles of 1–2 mm^3 explants are distributed in various vials containing that medium [3]. It is estimated that each vial contains about 15 particles of tissue, and the equivalent of two normal parathyroid glands, weighing 15–30 mg each, should be implanted [10]. Other authors recommend the use of Dulbecco's modified Eagle medium as final preservation medium [7, 11]. Dimethyl sulfoxide (DMSO) at a concentration of 10 % is added to the medium as a cytoplasmic stabilizer, as well as 10–30 % of autologous serum.

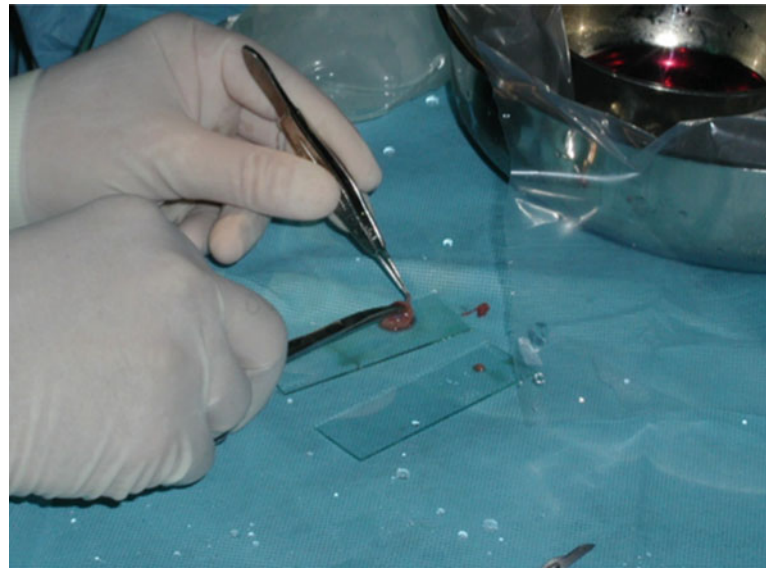

Fig. 34.1 Intraoperative defatting of the parathyroid tissue

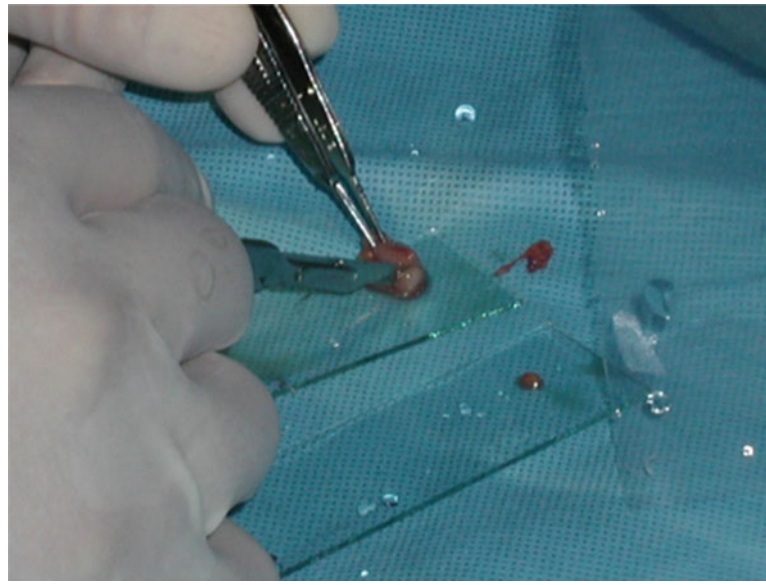

Fig. 34.2 Fragmentation of the parathyroid tissue

Regarding the cooling process, almost all authors agree that vials should be placed in a programmable freezer, that decreases the temperature from −1 to −80 °C. Once they have cooled, the vials are transferred to a liquid nitrogen freezer, where they reach a final temperature of −170 to −196 °C [2, 12].

As to the manner of performing cryopreservation and its timing, there is no universal protocol. An experience carried out by Santa Ritta Barreira et al. did not show changes in the ultrastructure of parathyroid samples stored for periods of up to 12 h in Dulbecco's medium (DMEM) before cryopreservation [8]. However, it is recommended to run the process as soon as possible after obtaining the tissue sample in the operating room. Several authors have found bacterial contamination in up to 23 % of samples; this reinforces the argument in favor of a swift processing [13].

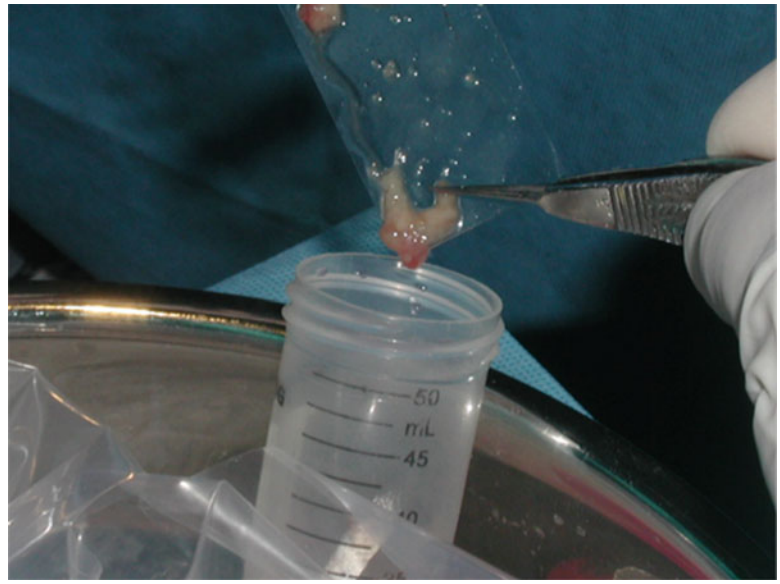

Fig. 34.3 Transportation to the laboratory in a tube with Dulbecco's modified Eagle medium

As to the thawing and preparation process, either for a structure and functionality "in vitro" experiments or for autoimplantation in a patient, the cryovials, according to the number of fragments needed, are quickly thawed in a water bath at 37 °C. Then they are washed three times with Hank's balanced salt solution (HBSS, Sigma®) at 37 °C, to remove the DMSO, before processing or implanting it under sterile conditions [14].

Assessment of Cell Viability and Parathyroid Function After Cryopreservation

The possibility of cryopreserving animal parathyroid cells preserving their morphology was demonstrated by Blumenthal and Walsh in 1950 [15]. Since that first experience, many authors have explored the possibility of stimulating "in vitro" and autotransplanting parathyroid tissue that had been cryopreserved for various time periods. But it was Brennan who for the first time showed that "in vitro" PTH suppression in the presence of high calcium concentrations in cryopreserved human parathyroid cells could be a good indicator of cell vitality and functionality before autotransplantation [15].

Therefore, two aspects should be considered. One is the preservation of cell function and structure after various periods of cryopreservation. Another is finding whether there is a maximum period of cryopreservation after which histological and functional characteristics begin to deteriorate.

Herrera, Grant, and Van Heerden published their experience in 1992, and showed that parathyroid cell morphology and functional activity were maintained, regardless of the duration of cryopreservation, up to a period of 24 months [9].

In 1997, Mc Henry, Stenger, and Calandro cryopreserved bovine tissue for periods of 1–52 weeks, comparing the number of viable cells per mg of cryopreserved tissue and the release of cytosolic calcium and parathormone in baths with extracellular calcium concentrations ranging from 0.5 to 3 mM. They compared a group of cryopreserved fragments of 1–2 mm^3 with another group of cells dispersed after treatment with collagenase. They concluded that cryopreservation, regardless of its duration, decreased the number of viable cells, and the functional response was better for tissue preserved as fragments than as dispersed cells [4].

In 2005, Cohen et al. observed that no parathyroid samples autotransplanted in humans were functional after a cryopreservation period longer

than 22 months. Marlon Guerrero et al. attempted to confirm such findings "in vitro" in 2008; among 501 samples cryopreserved between 1991 and 2006, they selected 106 at random (21 %), which were heated, centrifuged, and suspended in a medium containing 90 % of bovine serum and 10 % of DMSO, and finally stained with trypan blue to assess cell viability. Results obtained validated Cohen's observations, since samples cryopreserved for less than 24 months exhibited a 71 % viability, compared to 1 % seen in samples preserved for longer periods [9]. The strength of this study is that it examined a period of 15 years of cryopreservation; that is also its weakness, since preservation techniques have probably changed throughout that time.

Also, Alvarez-Hernandez et al., in 2008 published an investigation with samples, both fresh and cryopreserved, cultured during 60 h, obtained from 18 patients with secondary hyperparathyroidism. Cell viability was similar in fresh and cryopreserved samples after culture. However, cryopreserved samples exhibited worse secretory response of intact PTH (10 %) than fresh samples (60 %) when exposed to a medium with 0.6 mM of calcium compared to one with 1.2 mM. As to the inhibitory response of PTH when exposed to a medium with calcitriol, it was similar in both groups. Hence, the authors propose to use this test to select cryopreserved samples during the process of "in vivo" implantation [7].

In a very successful series of metachronous autotransplantation of tissue cryopreserved for an average time of 23 months (see comments on these results later), among 15 samples studied before transplantation only one exhibited a necrosis index of 70 %, whereas 14 exhibited a 100 % cell viability [3].

In our personal experience (unpublished to date), of the 216 samples stored in 2013 in a bank of cryopreserved parathyroid tissue, 15 that were no longer necessary for autotransplantation were examined. The 15 samples had been cryopreserved for 3–11 years, and several fragments of each one were analyzed. All samples were assessed for cell viability using H&E and Tunnel techniques before culture; subsequently they were cultured in a medium with 0.6 mM of calcium to determine secretion of intact PTH, and in another medium with 1.2 mM of calcium and 10^8 of calcitriol to study calcitriol receptors. A control group as well as a final sample were available to assess post culture viability. Overall results showed that cryopreservation did not alter cell viability, independently of the duration of preservation, and post culture viability was close to 80 %. Most samples were functionally able to secrete intact PTH and exhibited calcitriol receptors.

Later we will further discuss other authors' opinions related to the cost-effectiveness of maintaining an institutional bank of cryopreserved parathyroid tissue.

Evolution of Parathyroid Autotransplantation

Autotransplantation of fresh or cryopreserved parathyroid tissue is a common resource in modern surgery of thyroid and parathyroid disorders. It was described for the first time in human beings by Lahey [1].

In the case of thyroid surgery, whenever the surgeon has questions regarding vitality of the preserved parathyroid gland, immediate autotransplantation to the muscle cervical tissue is the rule. This approach applies particularly in cases in which dissection of the central compartment is indicated, especially regarding the inferior parathyroid glands, where vascularization is difficult to preserve.

For the treatment of primary hyperparathyroidism due to diffuse hyperplasia, it is usually recommended to preserve half of a well vascularized gland, preferably one of the upper glands (as we have already mentioned, cryopreservation is generally indicated for a potential metachronous autotransplantation).

In chronic renal patients, secondary hyperparathyroidism presents additional problems, and in recent years several lines of work have been proposed: subtotal parathyroidectomy (with less metabolic impact but higher chances of recurrence), total parathyroidectomy without autotransplantation (which offers better chances of

cure and relatively low recurrence rates), and total parathyroidectomy with autotransplantation, occasionally with additional thymectomy (here, recurrence rates are 80 % because of the autoimplanted graft). Obviously, the three variants must be accompanied by cryopreservation in case of an eventual deferred transplant. In 2007, a group of German universities started a prospective, randomized, and multicenter trial (TOPAR PILOT trial ISRCTN86202793), comparing the last two options mentioned. The trial has not recruited patients since 2013, and no results have been reported so far [16].

One European survey published in 2013 to assess the conduct of endocrine surgeons in cases of secondary HPT showed very heterogeneous results. Of the 86 surgeons who responded to the survey, 60 % performed more than 50 procedures for HPT per year, but only 37 % operated on more than 16 cases of secondary HPT annually. Although all the surgical procedures described were listed among the answers, differences among the various responders were marked. Among 72.7 % of the surgeons surveyed, immediate autotransplantation was the rule, but only 27.4 % of them performed cryopreservation [17].

The first reference to the use of cryopreserved parathyroid tissue dates from 1977 and was published by Wells, Gunnels, and Gutman, who used it to autotransplant a patient with secondary hyperparathyroidism 6 weeks after parathyroidectomy. Wells himself performed autotransplantation in 6 hypoparathyroid patients following surgery for primary hyperplasia, 2–6 months after the original surgery; functional results were adequate in 5 patients [18].

In 2006 the group of Menezes Montenegro and Ferraz published successful results in two renal patients with postoperative hypoparathyroidism, using tissue that had been cryopreserved for 21 and 30 months respectively. The two patients, followed for 3 and 6 years post autoimplantation, had normal serum calcium values and PTH levels of 37 and 95 μg/ml [18].

Agarwal et al. reported in 2013 the Cleveland Clinic experience with more than 2000 operations for hyperparathyroidism. They cryopreserved samples in 30 % of their population (multiglandular disease and parathyroid reoperations) and in 9 patients (1.5 % of cryopreserved samples and 1 % of the population) they performed deferred autotransplantation 3–22 months after the original operation. All patients normalized their calcemia and PTH levels and most experienced symptomatic improvement [10].

In our experience, of the 206 samples stored at our institution's cryopreservation bank, only 4 were used for patients who underwent autotransplantation. Our results have not been as positive as some reported by others, but we clearly saw normalization of calcemia and detectable PTH levels, with a decrease in the need for medical treatment in 50 % of cases.

Parathyroid Auto-Transplantation Technique

In case of a fresh autotransplantation, it can be performed after fragmentation into particles of 1–2 mm^3, either through open surgery or injection of the particles dissolved in saline solution [1, 19]. The former is the most popular technique.

During thyroid surgery, and after fragmenting the fresh parathyroid gland/s to be reimplanted into samples of 1–2 mm^3 (*histology is performed first to confirm the tissue's parathyroid origin*), the fragments are placed into two or three pockets made in a sternocleidomastoid muscle, taking care to avoid bleeding. It is usually recommended to mark the site with a nonresorbable suture. Some authors prefer to use the pectoralis major as a muscle bed, although it seems more rational to select a site in the neck [1].

In case of autotransplantation in a patient with hypoparathyroidism after surgery for secondary hyperparathyroidism, the preferred site is the nondominant forearm, where a longitudinal incision is made on the brachioradialis muscle. Considering that 20–40 fragments must be implanted, and that each muscle pocket will hold 3 or 4 of them, several pockets need to be created, and later marked and sealed with a nonresorbable suture or a metal clip [2]. The forearm offers the advantage of allowing an early assessment of the graft's function, by measuring PTH in both antecubital veins [10].

When the upper limb has to be preserved because of the need for arteriovenous fistulae, other recipient sites must be chosen, i.e., the pectoralis major, the deltoid muscle or even the presternal subcutaneous tissue [1]. The first two muscles, since they are larger, present a problem at the time of reoperating a patient due to recurrent, graft related hyperparathyroidism. Occasionally, we have had to resort to other techniques, such as alcohol injection treatment, to control hyperfunction of the implant [20].

Cost-Benefit of an Institutional Cryopreservation Bank

Although it is quite clear that having a bank for cryopreserved tissue represents a qualitative difference in service for the institution and its patients, many publications have questioned the cost-effectiveness of the procedure based on its low utilization rate.

In 2010, Borot et al. published a performance analysis from nine cryopreservation banks in France. The function of the implanted grafts was stratified in three levels: (1) Fully functional (normal calcium and PTH levels post implantation without the need for therapeutic replacement); (2) Partially functional (normal PTH levels but no treatment required to maintain normal calcemia); (3) Nonfunctional (low PTH levels and continuous treatment required).

For renal patients who underwent autotransplantation, the criterion was based on PTH levels in the antecubital vein of the nontransplanted forearm. (1) Nonfunctional: PTH levels below 20 μg/ml, with hypocalcemia and low PTH levels, requiring medication; (2) Partially functional: PTH levels 21–50 μg/ml, with hypocalcemia and normal PTH, requiring medication; (3) Fully functional: forearm PTH levels between 51 and 300 μg/ml, normal calcium and PTH levels, not requiring medication; (4) Hyperfunctional: PTH levels above 300 μg/ml with hypercalcemia. Among 1376 samples, only 22 were eventually implanted (1.6%). Moreover, that number of procedures was performed by 12 surgical teams and of the implanted grafts, 80% were nonfunctional. Hence, the authors recommend that cryopreservation should be performed only at highly experienced centers, and that material that has been cryopreserved for more than 1 year should be destroyed [5].

Schneider et al. whose excellent results have already been quoted, analyzed the high costs and lack of reimbursement by health insurance carriers, with a population at a global risk of hypoparathyroidism not exceeding 1.3%. Nonetheless, they emphasize the notion that for patients who require reoperation due to persistent HPT, or for patients undergoing total parathyroidectomy without fresh autotransplantation, cryopreservation should be mandatory [3].

Along the same lines, Shepet et al. reported that from a total of 2018 operations for hyperparathyroidism, cryopreservation was performed in 21% of cases. Only four patients required autotransplantation (1%) and only one of the four transplants was useful. Therefore, the authors question the financial viability of the project [12].

Additional Future Perspectives

Undoubtedly, having a bank of cryopreserved parathyroid tissue also opens the door for future allotransplantation. Although for a long time such procedure has been attempted, results so far have been scarce and heterogeneous.

Several authors have reported promising results with allotransplantation in patients who had already received one kidney and hence were immunosuppressed [21, 22]; allotransplantation performed simultaneously with the kidney transplant, from the same donor, has also been reported [23].

Regarding allotransplantation in patients who are not immunosuppressed, especially among those with hypoparathyroidism due to thyroid surgery, encapsulation with alginates of cryopreserved parathyroid tissue has been attempted, although results have been variable. In a case reported in 2009, using two phases of autotransplantation, normal calcemia was achieved and lasted 21 months, but subsequently, PTH levels dropped again [24].

We believe this is an issue that scientists will have to address in depth soon, to fight against the scourge of hypoparathyroidism, and for this purpose banks of cryopreserved tissue will undoubtedly represent a very helpful resource.

Summary

Cryopreservation of the parathyroid gland is indicated whenever a potential risk of permanent hypoparathyroidism is foreseen, given the serious metabolic consequences of such disorder. Most frequent indications are reoperations due to persistent or recurrent hyperparathyroidism, followed by total or subtotal resection of the parathyroid glands to resolve familial or sporadic forms of primary, secondary, or tertiary hyperparathyroidism. Success rates are lower than those obtained with fresh parathyroid tissue autotransplantation; transplant with cryopreserved tissue is functional in about 50 % of cases. Histological and functional exams allow assessing the preservation of cell histoarchitecture and the functional response of parathormone secretion. The best vitality rates are obtained when tissue is preserved for less than 24 months.

Society Guidelines

- Guideline for autologous tissue management. In: Guidelines for Perioperative Practice. Denver, CO: AORN, Inc; 2015:187–238. 2.

Best Practices: N/A

Expert Opinion

For a team of experts in parathyroid surgery, the availability of a cryopreservation bank contributes a qualitative difference to patient care. Although autotransplantation is performed in only a small part of the donor population, the benefits obtained are relevant for their impact on patients' quality of life. Additionally, having an institutional bank of cryopreserved parathyroid tissue allows investigators to perform experimental studies that can open a future path for successful allotransplantation.

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Treatment of Hypoparathyroidism

35

Priya Dedhia and Gerard Doherty

Contents

Introduction

Treatment for hypoparathyroidism is based on the acuity, symptoms, and pathogenesis. For years, the mainstay of treatment has been calcium, vitamin D metabolites and analogs, and thiazide diuretics. Recently, however, innovative therapies such as calcium sensing receptor (CaSR) inhibitors, parathyroid hormone (PTH) analogs, and cell- or tissue-based therapies have demonstrated similar efficacy to calcium and vitamin D analogs, but may result in fewer side effects and complications.

Goals of Therapy

Hypocalcemia as a result of hypoparathyroidism can result in severe symptoms such as seizures, tetany, laryngospasm, bronchospasm, cardiac arrhythmia, cardiomyopathy, impaired renal function, altered mental status, and bone malformation. Treatment for hypoparathyroidism aims to prevent or treat these symptoms while reducing the possible complications of hypercalcemia, hypercalciuria, and hyperphosphatemia. These complications resulting from treatment of hypoparathyroidism can contribute to cardiac arrthymia, nephrolithiasis, nephrocalcinosis, renal dysfunction, and basal ganglia calcifications. For this reason, treatment aims to maintain a serum

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albumin-corrected calcium level in the low normal range, serum phosphorus in the high normal range, 24 h urine calcium below 300 mg, and calcium-phosphate product below 55 mg^2/dL^2.

Acute Management

Acute hypoparathyroidism resulting from sudden decline in PTH and serum calcium can present as potentially life-threatening tetany, seizures, or cardiac arrthymia. This phenomenon can be seen after surgery, with an incidence ranging from 6.9 to 46 % following thyroid surgery [1–5]. Treatment for acute symptomatic hypoparathyroidism consists of bolus intravenous calcium gluconate (Table 35.1) followed by continuous infusion, which usually results in immediate relief of symptoms. Reversal of symptoms in congestive heart failure caused by chronic hypocalcemia is slow and requires additional therapy such as supplemental oxygen and diuretics [6–9]. In the presence of magnesium deficiency, magnesium is administered concomitantly. These patients require electrocardiographic monitoring and assessment of serum ionized calcium every 1–2 h until stabilized. Administration of oral calcium and the active metabolite of vitamin D, 1,25-dihydroxyvitamin D_3 (calcitriol), should be initiated as soon as feasible.

Chronic Management

Calcium

Patients with asymptomatic or minimally symptomatic hypocalcemia can be managed in the outpatient setting. Calcium carbonate and calcium citrate are widely accepted forms of calcium supplementation (Table 35.1). In general, studies on the bioavailability of calcium carbonate and calcium citrate demonstrate conflicting results depending on the population studied and the methodology [10–12]. Premenopausal women treated with calcium carbonate exhibited improved calcium bioavailability measured by serum total and ionized calcium and PTH compared to treatment with calcium citrate [12]. Studies in postmenopausal women have demonstrated no difference or superior bioavailability of calcium citrate [10, 11, 13]. In addition to menopausal status, gastric acid secretion may account for some of these differences. In the presence of achlorhydria or diminished gastric acid output, as can be seen with proton-pump inhibitors and H_2 blockers, calcium citrate provides superior bioavailability because calcium carbonate requires an acidic environment for absorption [14]. Calcium carbonate and calcium citrate contain 40 and 21 % of elemental calcium, respectively. In general, 1–2 g of elemental calcium is administered three times a day.

Table 35.1 Currently available treatment of hypoparathyroidism

Agent	Starting dose	Route	Use
Calcium gluconate	1–2 g	Intravenous	Acute hypoparathyroidism
Calcium salts	500–1000 mg of elemental calcium three times daily	Oral	Chronic hypoparathyroidism
Vitamin D metabolites	See table 35.2	–	–
Hydrochlorothiazide	25–100 mg daily	Oral	Hypercalciuria
Chlorthalidone	25–100 mg daily	Oral	Hypercalciuria
PTH 1-34	0.5–0.7 mcg/kg daily[a]	Subcutaneous	Chronic hypoparathyroidism
PTH 1-84	50–100 mcg daily	Subcutaneous	Chronic hypoparathyroidism

[a]Currently not approved for treatment of hypoparathyroidism

Vitamin D Metabolites and Analogs

In addition to calcium, treatment with vitamin D metabolites or analogs is critical in the management of hypoparathyroidism by improving intestinal calcium absorption and potentially by promoting bone remodeling ([15, 16]; reviewed in [17]). Vitamin D is available in several forms, which differ in onset of action, half-life, and cost (Table 35.2). Cholecalciferol (viamin D_3), which is cutaneously formed or obtained in the diet, has a half-life of approximately 20 h. Ergocalciferol (vitamin D_2), which is manufactured from yeast, has been used to treat severe vitamin D deficiency because historically it has been available in higher doses than cholecalciferol. However, several studies suggest that ergocalciferol is 3 times less potent, has a slower onset of action (3 days vs. 14 days) and has a shorter duration of action than cholecalciferol [18–21]. Calcidiol (25-hydroxyvitamin D_3), which is not commonly used for pharmacologic replacement, is produced by hydroxylation of cholecalciferol in the liver and has low biologic activity, but is the major metabolite in the bloodstream. Calcidiol is further hydroxylated in a PTH-dependent manner by renal 1α-hydroxylase in the kidney resulting in formation of the most active metabolite, calcitriol. Because of a rapid onset of action and no requirement for PTH-dependent conversion, calcitriol results in improvement of hypocalcemia within hours. The potency of calcitriol can result in hypercalcemia, however, this is quickly reversed upon discontinuation of calcitriol due to the short half-life of 4–6 h. Alfacalcidol (1-hydroxyvitamin D_3) and doxercalciferol (1-hydroxyvitamin D_2) are synthetic analogs that can be converted to calcitriol in the liver. Like calcitriol, alfacalcidol and doxercalciferol (1) do not require PTH-mediated activation, (2) have a rapid onset of action and short half-life, and (3) can induce hypercalcemia [22–26]. Doxercalciferol appears to be less prone to hypercalcemic episodes than calcitriol and alfacalcidol; however, these studies were performed in patients with secondary hyperparathyroidism and animals models, so their applicability to hypoparathyroidism is limited [26–28]. Prior to the availability of metabolically active forms of vitamin D, high doses of cholecalciferol or ergocalciferol were used to treat hypoparathyroidism with some success, perhaps due to (1) low affinity binding of cholecalciferol or ergocalciferol to the vitamin D receptor when supplemented at high doses and (2) limited conversion of cholecalciferol or ergocalciferol to calcitriol despite absence of PTH. At present, active metabolites of vitamin D are primarily used in the treatment of hypoparathyroidism. Cholecalciferol or ergocalciferol supplementation in addition to active metabolites of vitamin D may be beneficial because of a longer half-life and limited peripheral tissue-mediated conversion to calcitriol; however, further studies are needed to substantiate this possibility [29, 30].

Management of Calcium and Vitamin D-Related Complications

Most complications that occur due to treatment of hypoparathyroidism are related to vitamin D toxicity, which can result in hyperphosphatemia, hypercalcemia, and hypercalciuria. Vitamin D supplementation enhances intestinal absorption of calcium and phosphorus. If hyperphosphatemia occurs, initial treatment is to reduce dietary intake. Phosphate binders are reserved for severe situations. Hypercalcemia may be short-lived or prolonged depending on the form of vitamin D

Table 35.2 Vitamin D metabolites

Vitamin D preparation	Starting dose	Onset of action	Plasma half-life	Cost
Cholecalciferol	25,000 IU/d	8–72 h	14–25 h	$
Ergocalciferol	50,000 IU/d	10–24 h	19–48 h	$
Calcidiol	0.25 mcg/d	12 h	16–19 days	–
Alfacalcidol	0.25 mcg/d	6 h	3 h	$$
Doxercalciferol	1 mcg/d	Unknown	32–37 h	$$$$$
Calcitriol	0.25 mcg/d	2–6 h	3–8 h	$$

replacement. Hypercalciuria can occur in the absence of hypercalcemia due to poor renal calcium resorption [25]. Thiazide diuretics are used in prevention and treatment of hypercalcemia and hypercalciuria.

Thiazide Diuretics

Thiazide diuretics reduce urinary calcium excretion by increasing distal renal tubular calcium reabsorption (Table 35.1). Although some studies on surgical hypoparathyroidism suggested that this reduction of urine calcium is PTH-dependent [31–33], other studies indicate that decreased urinary calcium does not require presence of PTH [34]. Larger studies delineating the cause of hypoparathyroidism, the quantity of PTH, and the effect of thiazide diuretics are warranted. Until such studies are available, a trial of thiazide diuretics is indicated in hypoparathyroid patients with hypercalciuria. Thiazide diuretics are most likely to be beneficial in hypoparathyroid patients with activating CaSR mutations where treatment of hypocalcemia frequently results in hypercalciuria [35, 36]. In addition to serum calcium, potassium and magnesium levels should be monitored and supplemented if necessary. Treatment with a thiazide diuretic should be discontinued if it fails to reduce urine calcium or results in hypotension.

Calcilytics

Activation of the parathyroid CaSR results in increased intracellular Ca^{2+} and decreased PTH secretion. CaSR is expressed in parathyroid chief cells and in all nephron segments in the kidney. Activating CaSR mutations cause inappropriately low PTH levels in the setting of hypocalcemia. Although activation of renal CaSR primarily increases urinary calcium excretion, it also inhibits resorption of potassium, sodium, and water (reviewed by [37]). Calcimimetics potentiate the CaSR and inhibit PTH secretion and are useful in treatment of hyperparathyroidism whereas calcilytics inhibit the CaSR and can treat certain forms of hypoparathyroidism [38]. One of the early calcilytics, NPS 2143, reduced intracellular calcium in human embryonic kidney cells, stimulated PTH secretion from bovine parathyroid cells in vitro, and increased serum calcium in parathyroidectomized rats [38–41]. Because of promiscuous action against norepinephrine, dopamine, and serotonin monoamine transporters by NPS-2143, three other calcilytics, ronacaleret (SB-751689), NPSP795, and JTT-305/MK-5442, with a more desirable selectivity profile were developed. Ronacaleret administration in a randomized placebo-controlled trial of 569 postmenopausal women with osteoporosis resulted in increased serum calcium, PTH, and lumbar spine bone mineral density [42]. However, decreases in bone mineral density of the total hip, femoral neck, and trochanter were seen. The effects of ronacaleret in hypoparathyroidism have yet to be studied. Similarly, treatment with JTT-305/MK-5442 increased serum calcium, PTH, and bone formation markers in a randomized placebo-controlled trial on 383 postmenopausal women with osteoporosis [43]. NPSP795 is currently in Phase II clinical trials for treatment of hypoparathyroidism secondary to activating CaSR mutations. The efficacy of these medications in patients with hypoparathyroidism due to activating CaSR mutations will be critical because of the complications caused by calcium and vitamin D replacement, as well as the ineffectiveness of PTH replacement.

Synthetic PTH

Treatment of hypoparathyroidism with the standard agents of calcium and vitamin D leaves patients vulnerable to psychiatric illnesses and increased morbidity from infections while exposing patients to the risks of renal and vascular disease. A retrospective U.S. study of patients with hypoparathyroidism indicated increased risk of chronic renal insufficiency and hospital admission related to hypoparathyroidism [44]. Nationwide Danish case-control studies in patients with postsurgical hypoparathyroidism demonstrated a fivefold increased risk of renal stones and renal insufficiency, twofold increased incidence of depression or bipolar disease, and

increased risk of hospitalizations due to infection or seizure [45, 46]. In nonsurgical hypoparathyroidism, there was an increased risk of renal insufficiency, cardiac ischemia and arrhythmia, stroke, depression, and hospitalization due to infection in a similarly structured Danish case-control study [47]. One small case-control study demonstrated that intimal thickening of arteries was elevated in patients with hypoparathyroidism suggesting intimal thickening as a mechanism for risk of cardiovascular disease [48]. Together, these data imply that treatment of hypoparathyroidism with calcium and vitamin D cannot adequately replace PTH. Thus, interest in PTH replacement therapy has increased. Currently available pharmacologic replacement therapies include recombinant human PTH 1-34 and PTH 1-84 (Table 35.1, Fig. 35.1). Both proteins must be administered subcutaneously due to poor oral bioavailability.

Bovine PTH

Bovine PTH was first used to treat hypoparathyroidism in 1929. This treatment resulted in neutralizing antibodies limiting further therapy [49, 50]; however, these studies paved the way for treatment with recombinant human PTH.

PTH 1-34

Initial studies on PTH replacement were performed using the biologically active N-terminus of the PTH molecule (Fig. 35.1). One case study demonstrated increased serum calcium after treatment with PTH 1-38 [51]. Subsequent studies used PTH 1-34. A small 5-month pilot study randomized ten patients with hypoparathyroidism to daily subcutaneous PTH 1-34 injections or calcitriol. Those patients treated with PTH 1-34 demonstrated normal serum calcium and decreased urinary calcium suggesting superiority compared to calcitriol [52]. These results were confirmed in a 3-year randomized control trial of 27 patients with hypoparathyroidism [53]. Urine calcium was reduced with PTH 1-34 treatment, but this was not statistically significant, likely due to small sample size. This study also demonstrated no differences in bone mineral density, although markers of bone mineral turnover were increased with PTH 1-34 treatment. Additional studies by the same group demonstrated that titration of PTH 1-34 dose to twice daily dosing or continuous dosing via pump resulted in uniform serum calcium and further reduction of urinary calcium compared to daily dosing regimens [54, 55].

Unfortunately, long-term supraphysiological doses of PTH 1-34 given to rats with normal functioning parathyroid glands led to osteosarcomas [56]. This risk was not recapitulated in postmenopausal women who were given PTH 1-34 for 2 years for the treatment of osteoporosis [57]. Furthermore, a trial of 12 pediatric patients with hypoparathyroidism treated with twice-a-day PTH 1-34 for 3 years vs. calcitriol, which was

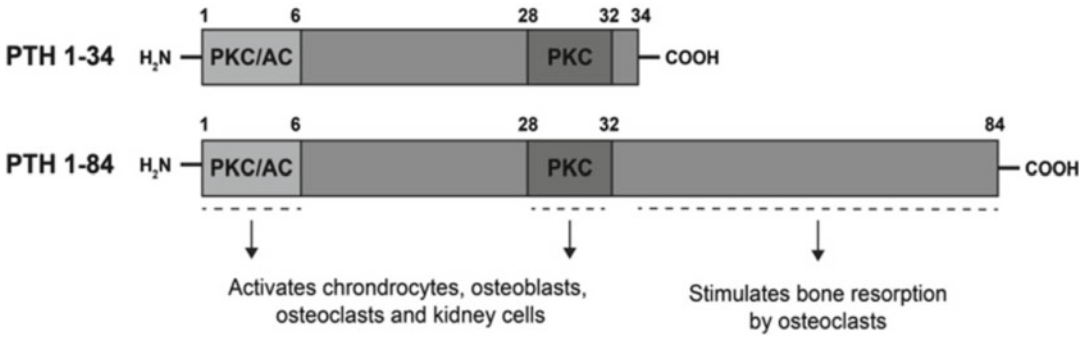

Fig. 35.1 Recombinant human PTH. PTH 1-34 and PTH 1-84 both contain two protein kinase C (PKC) domains and an adenylate cyclase (AC) domain, which are located in the N-terminus. PKC and AC activate the PTH receptor on chondrocytes, osteoblasts, and kidney cells. Only PTH 1-84 retains the C-terminus, which may stimulate bone resorption by osteoclasts through an alternative receptor

initiated prior to the toxicology studies in rats, demonstrated no differences in serum or urine calcium, bone mineral density, growth, or adverse events including development of osteosarcoma during the 3-year follow-up [58].

Despite these findings, enthusiasm for long-term use of PTH 1-34 for hypoparathyroidism, especially in pediatric populations, has waned. Currently, use is restricted to treatment of osteoporosis in adults for no more than 2 years. Surveillance studies to identify the risk of osteosarcoma with long-term (15 years) use in adults are ongoing, and interim results demonstrate no risk of osteosarcoma [59]. The final report is expected to be available in 2019.

PTH 1-84

A case series of 30 hypoparathyroid patients using PTH 1-84 demonstrated decreased requirements for calcium and vitamin D metabolites [60]. This study showed no decrease in urinary calcium but did identify an increase in bone mineral density at the lumbar spine. These findings were confirmed in a randomized double-blind trial of 62 female patients with post-surgical hypoparathyroidism in which PTH 1-84 or placebo was added to a regimen of calcium and a vitamin D metabolite [61]. As expected, use of PTH 1-84 significantly reduced calcium and vitamin D metabolite requirements. Treatment with PTH 1-84 resulted in more episodes of hypercalcemia than placebo; however, this is likely due to lack of supplement titration until patients developed hypercalcemia. Although there was an initial increase in urine calcium with PTH 1-84 compared to placebo, no difference was noted for the remainder of the study. Furthermore, this study demonstrated a decrease in bone mineral density in the whole body, spine, and femoral neck in patients receiving PTH 1-84. A larger Phase 3 randomized placebo-controlled double-blind trial of 134 hypoparathyroid patients confirmed reduction of calcium and vitamin D supplementation with PTH 1-84 treatment and showed similar adverse events with PTH 1-84 compared to placebo [62]. Both placebo and PTH 1-84 treated groups demonstrated a decreased in urine calcium, but, surprisingly, the decrease from baseline in the placebo group was significantly greater than the PTH 1-84 group. Although these studies suggest limited renal protection by PTH 1-84, a recent open label study of 7 patients who received a single dose of PTH 1-84 demonstrated 12–26 % reduction of urine calcium and increased creatinine clearance compared to baseline parameters while on calcitriol [63]. Further studies are necessary to determine if PTH 1-84 will reduce the risk of nephrolithiasis and renal insufficiency. One 5-year open label study demonstrated improved quality of life with PTH 1-84; however, a subsequent 6-month randomized controlled trial demonstrated no improvement in quality of life [64, 65]. Again, additional long-term studies are warranted to determine if PTH 1-84 confers protection against psychiatric disease. Similarly, studies will be necessary to identify cardiovascular protection afforded by PTH 1-84. In these future studies, it will be important to analyze outcomes after patients are classified by surgical and nonsurgical hypoparathyroidism, given that risks may vary between these patient populations [45–48].

Initially, the N-terminus of the PTH protein was considered to be the biologically active fragment; however, mounting evidence suggests that the C-terminus also contributes to PTH function. Recombinant human PTH 1-84 and PTH 1-34 demonstrate slight differences in pharmacokinetics—half-life (1 vs. 1.5 h), peak post injection (0.5 vs. 1-3 h), calcium peak (4-6 vs. 6-8 h), and return to baseline calcium (16-24 vs. 24 h) [66–68]. Because of these structural and pharmacokinetic differences between PTH 1-34 and PTH 1-84, differences in treatment of hypoparathyroidism may be anticipated. A meta-analysis, which demonstrated 64 % risk reduction of vertebral fracture and increased spine bone mineral density in osteoporotic patients with use of either PTH 1-34 or 1-84, was unable to identify superiority of either hormone type [69]. To date, however, no comparative clinical trials have been performed.

Tissue and Cellular Transplants

The ideal treatment for hypoparathyroidism in most patients is replacement of functional, calcium-responsive parathyroid tissue. Although PTH hormone replacement therapy may provide some benefits over treatment with calcium and vitamin D, dosing regimens are still not physiologic. Several clinical and experimental models for transplantation of parathyroid tissue exist to prevent and treat hypoparathyroidism. Autotransplantation is performed in patients routinely, whereas allotransplantation is less common because of potential need for immunosuppression. Stem cell-derived parathyroid cells may offer restoration of physiologic parathyroid function in the future.

Autotransplant With and Without Cryopreservation

Hypoparathyroidism is most commonly secondary to neck surgery. Devascularization of the parathyroid glands can be intentional or unintentional. In the event of intentional devascularization or unintentional devascularization of the parathyroids identified intraoperatively, the parathyroid gland can be autotransplanted. In this scenario, the parathyroid gland is inspected for abnormality then placed in iced saline until the end of the operation. The gland is cut using fine scissors to create a suspension. The suspension is then implanted into a pocket created in the sternocleidomastoid muscle. An early case series consisting primarily of patients with secondary hyperparathyroidism demonstrated graft survival in 93 % of the 29 patients receiving autotransplants [70]. A later case series, in which autotransplantation of 1-2 parathyroid glands was routinely performed in conjunction with in situ preservation of remaining parathyroids, demonstrated normal long-term parathyroid function in 99 % of patients [71]. Function can reappear weeks to months after autotransplant. In general success rates vary from 85 to 99 % [72].

In addition to immediate autotransplantation, parathyroid tissue can be cryopreserved for transplantation at a later date. Cryopreservation can be considered in patients with hyperparathyroidism due to multigland disease where extent of resection may not be clear or likelihood of reoperation is high as with secondary and tertiary hyperparathyroidism (reviewed in [73]). In addition, extended dissection, repeat surgery, and thyroid malignancy were risk factors for postoperative hypoparathyroidism [74, 75]. Thus, cryopreservation in conjunction with autotransplantation can be considered in these situations. Cryopreservation is performed by dissecting parathyroid tissue into $1 \times 1 \times 1$ mm fragments followed by placement in iced saline. After transport, the supernatant is decanted and the tissue is resuspended in freeze media typically consisting of 80 % RPMI 1640, 10 % fetal bovine serum, and 10 % dimethyl sulfoxide [76]. Reimplantation is performed in the nondominant forearm so that graft function can be determined by comparing blood from antecubital veins of the grafted and nongrafted arms. Cryopreservation retains function in less than 60 % of patients whereas immediate autotransplant retains function in over 90 % of patients [77–79]. Thus, autotransplant should be performed in place of or in conjunction with cryopreservation when feasible.

Allogeneic Transplants

The first successful allotransplantation of parathyroid tissue was performed in a patient who underwent subtotal parathyroidectomy for secondary hyperparathyroidism [80]. After renal transplant, she developed hypoparathyroidism, which was corrected with parathyroid allotransplant from another patient undergoing parathyroidectomy for secondary hyperparathyroidism. Additional studies confirmed the feasibility of parathyroid allotransplantation in the setting of immunosuppression [81–85]. However, for the majority of hypoparathyroid patients, the risk of immunosuppression outweighs the risk of parathyroid allograft. Thus, several models have been generated to reduce the immunogenicity of parathyroid allografts. Parathyroid tissue cultured in vitro and depleted of antigen presenting cells was used for allotransplantation and resulted in tissue survival for up to 18 months

[86–89]. Nude mice have been used as an "interim host system" to condition human parathyroid tissue prior to allotransplantation, resulting in allograft function for up to 15 months post transplant in 2 patients [90]. More recent studies have adopted the technique of microencapsulation used in pancreatic islet cell transplantation [91–95]. Two patients receiving microencapsulated transplants demonstrated graft function 3 months after allotransplantation [96]. Another case report using microencapsulation demonstrated over 20 months of allograft function [97]. Translating the technique of microencapsulation from animal models to human allograft transplantation has met challenges. However, new approaches incorporating further modifications to the microcapsule generation are promising. A clinical trial, which is currently underway, will provide additional details regarding long-term viability of parathyroid allografts.

Stem Cell-Derived Therapy

Replacement of functional parathyroid tissue would provide the most physiologic treatment for hypoparathyroidism. Recent advances in allograft transplantation provide one avenue for cure; however, tissue sources for allogeneic transplantation may be pathologic or limited in availability. Developing a source of autologous PTH-producing cells from easily accessible tissue can obviate the constraints of contemporary treatment for hypoparathyroidism. Parathyroid organogenesis is carefully orchestrated by the actions of a network of transcription factors and signaling molecules that act on the pharyngeal endoderm and surrounding mesenchyme. A combination of human disorders associated with the parathyroid glands as well as murine experimental models have led to a greater understanding of this process. Several transcription factors critical to parathyroid development, such as Hoxa3, Pbx1, Pax1, Pax3, Pax9, Eya1, Six1, Tbx1, Gcmb (Gcm2 in mice), Aire1, and Gata3, have been identified [98–119]. Pharyngeal endoderm expresses Tbx1, Pax1, Pax9, Six1, Eya1 as well as Hoxa3 in the caudal region of the second pouch. These factors are important in specification of the third pharyngeal pouch and its derivatives including the parathyroid. Gata3 is required for expression of Gcm2, which is required for and specific to parathyroid organogenesis. Furthermore, many of these transcription factors can be used as markers of progenitor cell specification to the parathyroid lineage prior to differentiation into PTH-producing cells.

To date, parathyroid-like cells have been generated from embryonic stem cells (ESCs) as well as thymocytes, which share developmental origin with the parathyroid glands ([120]; reviewed in [121–124]). The Bingham protocol differentiates ESCs into definitive endoderm and then into PTH-producing cells using Activin A and increasing concentrations of fetal bovine serum for 5 days followed by removal of Activin A [120]. This protocol results in expression of Eya1, Six1, Pax1, GCM2, CaSR, and PTH [120]. Addition of sonic hedgehog appeared to increase CaSR and PTH mRNA expression, but did not increase PTH secretion [123]. A more complicated regimen of sequential treatment with BMP4/ROCK inhibitor, Activin A/BMP4/bFGF, NOGGIN/TGF-β pathway inhibitor, WNT3a/KGF/FGF10, BMP4/EGF, and FGF8 also resulted in *GCM2* mRNA expression [122]. Studies have shown that human thymocytes express low levels of *GCM2*, *CaSR*, and *PTH* mRNA [124]; however, this may be due to the presence of low numbers of parathyroid cells retained in the thymus [125]. Separation of thymic epithelial cells and treatment with the Bingham protocol resulted in increased *EYA1*, *GCM2*, *PAX1*, *CaSR*, and *PTH* mRNA expression [124]. Furthermore, long-term culture of these cells resulted in calcium-responsive secretion of PTH. These transdifferentiated thymocytes produced supraphysiologic levels of PTH. Although transplantation into immunocompromised *Rag2−/−* mice did not result in tumorigenesis, hypercalcemia as a result of hyperparathyroidism was not assessed [124]. These studies hold great promise for parathyroid organogenesis and treatment of hypoparathyroidism; however, future research is still necessary to demonstrate function in parathyroidectomized murine models.

Treatment of Hypoparathyroidism During Pregnancy

Maintenance of calcium homeostasis is essential for normal fetal development. Hypocalcemia attributable to undertreatment of hypoparathyroidism during pregnancy can result in fetal hyperparathyroidism, bone malformation, and death [126, 127]. Overtreatment resulting in maternal hypercalcemia can cause fetal parathyroid hypoplasia and miscarriage. During pregnancy, normal maternal calcium levels are maintained despite calcium mobilization to the fetal skeleton due to elevated levels of vitamin D metabolites and PTH related protein [128, 129]. Calcitriol requirements may be reduced or increased in the pregnant hypoparathyroid patient [126, 130–136]; however, calcitriol requirements generally decrease during lactation [130–132, 134, 137]. Historically, calcitriol was withheld during pregnancy due to concern for teratogenicity; however, recent studies have suggested that this is unlikely [126, 138]. Because of fluctuating calcitriol requirements, serum calcium levels should be assessed frequently during pregnancy and lactation. Generally, calcitriol requirements return to baseline after cessation of lactation.

Summary

Acute and chronic hypoparathyroidism can result in cardiac, renal, and psychiatric disease. Acute treatment consists of intravenous calcium gluconate. The mainstay of chronic treatment consists of calcium and calcitriol. Thiazide diuretics can be used to mitigate calciuria and nephrolithiasis. Calcilytics, which are not yet widely available for treatment of hypoparathyroidism, offer the potential for improved calcium homeostasis and fewer complications, especially to patients with activating *CaSR* mutations. Hormone replacement therapies such as PTH 1-34 and PTH 1-84 may offer advantages over calcium and calcitriol; however, further studies are required to characterize potential renal protection by reduction of hypercalciuria. Autologous parathyroid transplant is frequently used when risk of hypoparathyroidism is deemed to be high preoperatively or intraoperatively. In general, immediate autotransplant is more successful than transplant after cryopreservation. Conversely, allogeneic parathyroid transplants have not shown long-term success, except in the setting of immunosuppression. Future studies should focus on generation of functional parathyroid cells from autologous sources such as pluripotent stem cells or thymus. Significant work remains to demonstrate that these cellular therapies are functional in vivo, and do not result in hyperparathyroidism. However, parathyroid organogenesis provides the possibility of freedom from complications and permanent cure.

Society Guidelines: See ref. [139, 140]

Best Practices: N/A

Expert Opinion

Treatment of hypoparathyroidism is an infrequent but potentially intense endeavor. It requires the providers attention to detail and a high level of patient education and cooperation. Advances in hormone replacement therapy, auto transplantation, and the possibility of stem cell therapy offer hope to this population of patients.

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Intraoperative Nerve Monitoring for Parathyroid Surgery

36

Joseph Scharpf and Gregory Randolph

Contents

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Introduction

There exists an extensive body of literature examining the value of intraoperative recurrent laryngeal nerve monitoring (IONM) during thyroid and parathyroid surgery. These studies have advanced the understanding of electrophysiologic nerve monitoring and culminated in the publication of an international standards guideline statement. Most studies, though, have been an admixture of both thyroid and parathyroid surgical cases with varying indications in which parathyroid surgical cases represent the minority of cases. This chapter reviews the value of intraoperative nerve monitoring with a specific interest in its application regarding parathyroid surgery.

Electrophysiologic Recurrent Laryngeal Nerve Monitoring

Rationale for Monitoring

The location of the recurrent laryngeal nerves (RLN) adjacent to the thyroid gland and in close anatomic proximity to the parathyroid glands leads to the risk of RLN injury either from a rare parathyroid carcinoma disease process (Fig. 36.1) or during parathyroid surgery, most commonly performed for nonmalignant hyperparathyroidism. Injury rates to the RLN can vary significantly

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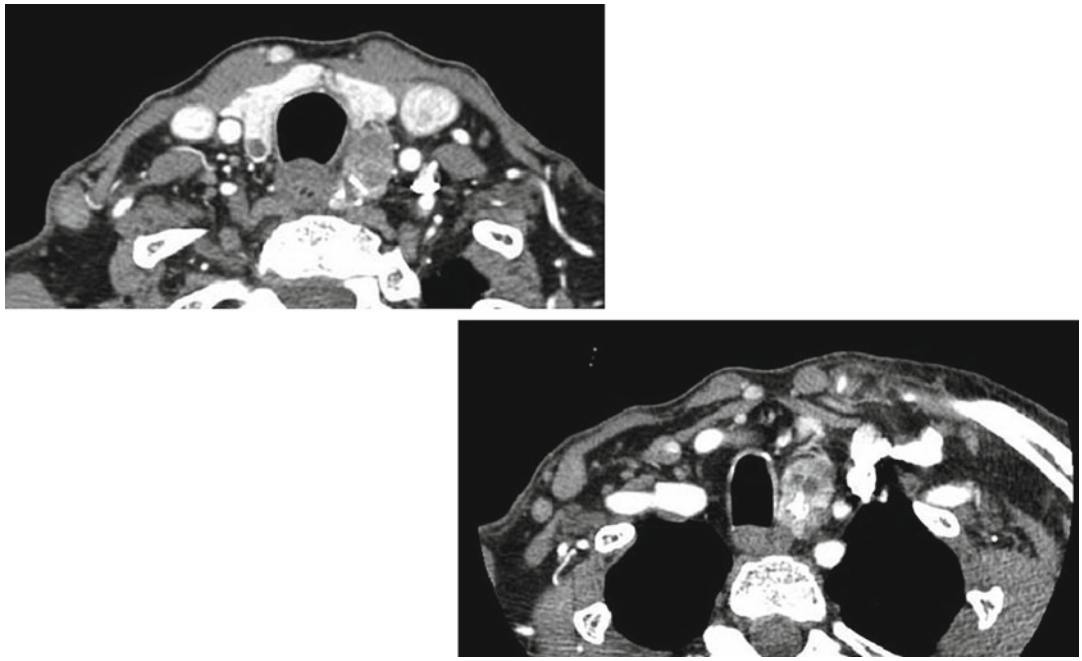

Fig. 36.1 Left inferior gland parathyroid carcinoma

among surgeons, but the rate of permanent RLN injury after initial surgery for primary hyperparathyroidism (HPT) has been consistently lower than 1 % in large retrospective studies that have originated from experienced centers [1, 2]. Concern has been raised that the rate is most likely higher when performed by less experienced surgeons [3]. Complications in the reoperative setting are more common secondary to extensive scarring, obfuscation of dissection planes and anatomic relationships, and proximity of the disease that necessitates reoperation to the RLN [4].

Temporary hoarseness can occur after any surgery that involves general anesthesia, but the potential for RLN injury in parathyroid surgery mandates greater concern when hoarseness occurs after this type of procedure [5]. The other nerves of major interest, which are frequently less directly addressed during parathyroid surgery, are the bilateral superior laryngeal nerves (SLN), injury to which can impair the ability to change pitch and reduce voice projection [6]. The obvious result of vocal fold paralysis (VFP) is loss of voice. In addition, debilitation can result from dysphagia and aspiration; an important role of the larynx is to achieve tight vocal fold closure necessary for normal swallowing. Shortness of breath and exercise intolerance can also result from this lack of closure necessary to Valsava [7]. Finally, the most dreaded of concerns is the life-threatening loss of airway patency and respiratory distress if a bilateral injury were to occur that would potentially necessitate a tracheostomy.

There has been a recent report looking at the impact of unilateral or bilateral (VCF) following thyroid surgery. The cost analysis could be similarly applicable to patients sustaining injury after parathyroid surgery. Seventy six patients who sustained either unilateral or bilateral (VCF) were compared to 238 patients who did not have injury during thyroid surgery. The two groups are matched to age, sex, race, and type of procedure. The authors found that, "patients who suffer a unilateral or bilateral VFP after undergoing thyroidectomy experience significantly more morbidity than similar patients who do not have VFP after thyroidectomy. The VFP patients incurred significantly more charges for health care in the first 90 days after surgery ([8]; Benninger et al. 2015)."

The avoidance of nerve injury in parathyroid surgery is centered on injury prevention measures that begin not during surgery but rather at the time of the initial evaluation of the patient. This evaluation is coupled with intraoperative and postoperative management decisions that optimize patient outcome. A detailed history, review of pathology, outside surgical records if applicable, and review of surgical indications with the patient and family are necessary to assess risk for any patient being considered for parathyroid surgery.

Experienced surgeons with low nerve complication rates are guided by principles to which they adhere with great discipline. Meticulous hemostasis throughout the surgical procedure cannot be overemphasized. It affords the surgeon with a clear view, often aided with loupe magnification, of the operative field to identify critical anatomic landmarks that lead to the identification of the RLN [7]. Recurrent laryngeal nerve visualization is currently considered the gold standard for nerve preservation [9]. It is associated with a lower risk of RLN palsy [10, 11].

The precise handling of tissue around the nerve to prevent stretch or traction injury on the nerve is of utmost importance. There is limited data in the literature to suggest that approximately 10 % of nerves that are traumatized are visually identified and appreciated as injured by the surgeon [3]. This places further emphasis on the importance of tissue handling and management of hemostasis. Nerve transection, which would generally be appreciated by surgeons who routinely identify the nerve, the standard for nerve protection, may not be as common of a contemporary reason for nerve injury.

Unique Circumstances in Parathyroid Surgery

Parathyroid surgery, in general, is an elective procedure without the acute threat of morbidity or mortality associated with malignancy. While guidelines exist for surgical candidacy, many patients present in an asymptomatic or low symptom profile state secondary to incidental blood testing that led to the diagnosis of hyperparathyroidism. This often healthier population carries an expectation for a lower treatment complication rate than that associated with other conditions. Although nerve identification is a routine practice for most surgeons during thyroid surgery, the same assumption cannot be extrapolated to parathyroid surgery. Many experienced and high-volume parathyroid surgeons do not routinely find the RLN nor certainly the SLN in each case. A particularly vulnerable and common area for nerve injury during thyroid surgery is at the ligament of Berry, where an extralaryngeal RLN bifurcation is susceptible to nerve injury [12]. This particular area does not have the same significance in parathyroid surgery, where the parathyroid gland does not have to be removed off the trachea at the ligament of Berry and thus does not place the nerve at the same level of risk for heat, traction, or transection risk. Recommendation has been made for surgeons though to have a low threshold for identifying the RLN during parathyroid surgery [13, 14]. There is no substitute for identifying the nerve to reduce inadvertent nerve injury rates [15].

Nevertheless, as discussed elsewhere in this book, changing practice patterns with evidence-based support for directed parathyroid surgery utilizing very small incisions, minimally invasive endoscopic approaches, or even remote access approaches does raise the concern for potential RLN or SLN nerve injury due to limited exposure for dissection. This risk is compounded by the aforementioned minority of nerve injuries that are even appreciated by surgeons intraoperatively. Recurrent laryngeal nerve monitoring may be valuable in identifying and confirming the location of the RLN [16, 17]. Because the frequency of RLN injury is low among experienced surgeons, who are a primary source of evidence-based surgical studies examining IONM, it is difficult to adequately power studies to provide evidence of its value in preventing nerve injuries [10, 18]. Furthermore, many experienced surgeons may commonly perform routine parathyroid procedures under local anesthesia because they believe the risk of nerve injury is quite low and the clinical scenario would not warrant IONM.

An interesting recent publication has examined the anatomic proximity of parathyroid tumors to the RLN in patients with primary hyperparathyroidism undergoing parathyroidectomy [16]. This is unique from much of the literature that primarily combines both thyroid and parathyroid patients. In this prospective study consisting of 136 patients with primary hyperparathyroidism, IONM was used to confirm RLN identification and to record the distance from the anatomically confirmed RLN to the parathyroid tumor. The findings confirmed that the RLN often lies in close proximity to the parathyroid adenoma at an average of just 0.52 cm, with tumors of the right upper position most commonly abutting the nerve compared to other positions. The tumors in the right upper position were on average only 0.25 cm from the nerve with 47 % of the tumors in the right upper position abutting the nerve [16]. This may clearly have implications for a personalized approach with consideration for IONM for tumors in this area if a directed approach is taken.

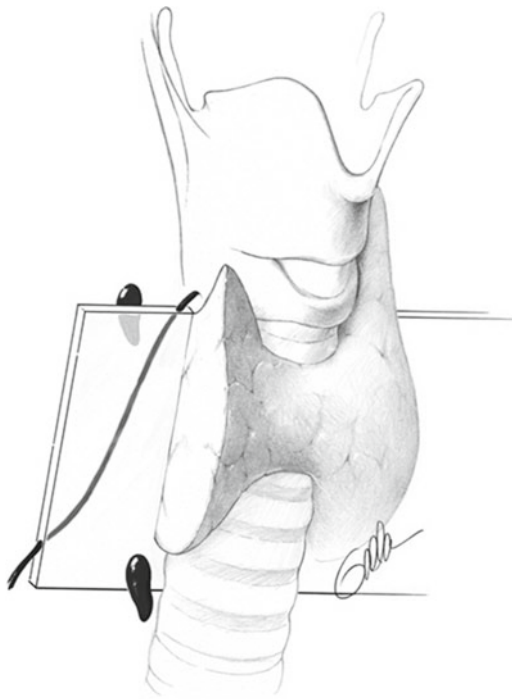

Fig. 36.2 Relationship of recurrent laryngeal nerve to parathyroid glands

Other circumstances that may also demand consideration for IONM during parathyroid surgery may include difficult parathyroidectomy procedures such as reoperations. The superior parathyroid gland develops in an embryological position posterior to the RLN when viewed in a sagittal plane (Fig. 36.2). Therefore, large superior parathyroid glands and inferiorly descended, ectopic superior thyroid glands behind the RLN in the retroesophageal region may place the RLN at a greater risk. Further consideration should be given for missing parathyroid glands, nonlocalizing preoperative imaging studies, prior neck surgery for spine surgery, trauma or any other reason, morbid obesity, or other patient anatomic factors creating exposure difficulty. These factors can certainly increase technical difficulty and have been shown to increase the rate of RLN injury [12]. IONM can be complimentary and beneficial to direct anatomic visualization of the RLN and perhaps even the SLN if an ectopic gland exploration would demand dissection that could potentially place it at risk (Fig. 36.3).

Expected Value of Nerve Monitoring for the Intraoperative Decision Process

The International Neural Monitoring Study Group, a multidisciplinary international group of surgeons and researchers dedicated to thyroid and parathyroid surgery, and neural monitoring, had proposed three modes listed below for IONM application that are relevant for parathyroid surgery [18].

Identification of the RLN

The application of intraoperative neural monitoring can assist in neural mapping using the neural monitor probe to electrically map the course of the nerve in the paratracheal region. Success for nerve identification rates between 98 and 100 % has been reported in multiple studies [19]. The use of the RLN nerve monitor does not prevent nerve injuries but is an excellent adjunct that may be helpful.

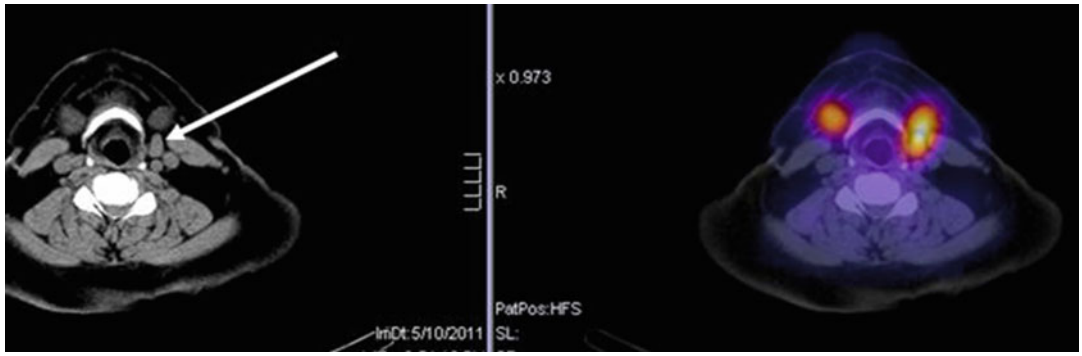

Fig. 36.3 Ectopic left parathyroid gland

Several large studies have compared a monitored group of patients and a nonmonitored group to determine if there was a difference in RLN injuries. These studies contained both thyroid and parathyroid surgeries with the majority of patients undergoing thyroid surgery. The documentation of proof that the use of nerve monitoring prevents nerve injury has been elusive for the previously stated reasons, especially for experienced surgeons with low complication rates. This may not be applicable to surgeons in general who perform these procedures. One of the largest of the series was a multi-institutional prospective nonrandomized study of over 16,000 patients who underwent thyroidectomy. The authors concluded that there was no statistical significant difference between visual identification alone and combined visualization with RLN monitoring [10]. Because of the unique circumstances of parathyroid surgery, it is even more unclear and difficult to power a similar study to examine a difference in nerve injury rates for monitored versus unmonitored patients in just parathyroid surgery. It is clear, however, that nerve monitoring will not turn an unsafe surgeon into a safe surgeon [20] and thus the aforementioned points of meticulous technique must always be respected.

Aid in Dissection

After identifying the nerve, stimulation applied in intermittent fashion could provide feedback to assist the dissection. This could be particularly valuable in a reoperative setting to trace the nerve's course through scar that obscures the field and allow for its dissection off the parathyroid tumor. In a study examining intraoperative electromyographic monitoring of the RLN in reoperative thyroid and parathyroid surgery, 52 cervical re-exploration procedures were performed with electromyography. Thirty one percent of the procedures were for parathyroid conditions (1 parathyroid carcinoma) and this group was compared to a nonmonitored group with similar characteristics. The monitoring did not decrease RLN complications in the study, but the authors did state that locating the RLN was generally not the source of injury, but rather resection of close disease placed the nerve most at risk [4]. The potential to dissect through these obscured planes with close disease utilizing neural monitoring as an adjunct could be valuable.

Neural Function Prognostication

The functional information provided by IONM could be invaluable to the physician who has seen a visually intact nerve but wants further support of its functional status before proceeding to the contralateral side for a four gland exploration. Dissection on the contralateral side could place the other nerve at risk, potentially resulting in a compromised airway at the end of an elective procedure. In other words, a nerve that is compromised on one side may give the surgeon pause to continue on and lead him or her to stage the

procedure once an expected return of function on the compromised side has occurred. It would also allow for investigation of the nerve for potentially treatable injuries that would include a crush injury from a suture tie or clip or lead to a primary repair of a discovered transected nerve that had not been appreciated during the initial dissection.

Prevention of bilateral paralysis is perhaps the most important application of IONM. Prior to neural testing there had been no other mechanism to accurately identify the location of nerve injury. Excellent evidence exists that final evoked potential amplitudes on intraoperative electromyography of the RLN correlates with immediate postoperative vocal fold function after thyroid surgery [21, 22]. In this study, the immediate postoperative vocal cord paralysis experience was reviewed when an EMG amplitude of less than 200 μv was set as a cutoff. The sensitivity, specificity, positive and negative predictive values, and accuracy at this level for vocal cord paralysis were found to be 95.5 %, 99.2 %, 72.4 %, 99 %, and 99.1 % respectively. This could certainly be applicable in parathyroid surgery. It would be of great value to the surgeon to alert him or her to the complication before it was clinically evident and therefore allow for preparations to be made, especially if it involved securing a compromised airway.

Although the routine use of neural monitoring in parathyroid surgery is controversial, there are clinicians who are proponents of its routine use to benefit patients. Expert opinion has advocated that neural monitoring be performed routinely because difficult cases cannot always be predicted preoperatively. The routine use of monitoring will allow for an advancement in the learning curve for surgeons so that they have greater experience in signal interpretation and troubleshooting [18, 23].

Technique and Equipment

The technique and standards of equipment for electrophysiologic monitoring of the RLN has been comprehensively outlined in the International Standards Guideline Statement from the International Neural Monitoring Study Group [18]. This document further provides an algorithm for evaluating the loss of signal during monitoring and for troubleshooting (Fig. 36.4). Importantly, normative intraoperative electrophysiologic waveform analysis has also been published for both the superior laryngeal nerve external branch and recurrent laryngeal nerve in patients undergoing thyroid surgery [24]. It is incumbent upon the surgeon to be familiar with the techniques available, equipment, and normative values of IONM to gain the desired level of predictive information regarding postoperative RLN function.

Preconditions

Optimization of IONM is contingent upon several elements that have been outlined by the International Neural Monitoring Study Group [18]. These elements include preoperative laryngoscopy in all cases. One of the main values of IONM is to provide information regarding the functional status of the vocal cords; therefore, the baseline status should be known before surgery. Attention should be paid to the vocal exam with a recommendation to strongly consider viewing the vocal folds by indirect laryngoscopy or flexible laryngoscopy for every patient in which surgery is contemplated. Recently multidisciplinary guidelines, "Clinical practice guideline: Improving voice outcomes after thyroid surgery," have been developed to address voice outcomes in relationship to thyroid surgery [25] and could also be readily applicable to any contemplated parathyroid surgery. This guideline focused on how to address the patient with disordered voice before and after thyroid surgery. The voice could be remarkably normal to perception even in the face of a nerve compromise resulting in vocal fold immobility. This may result in alterations in surgical planning and preparation. Understandably, is also important to perform a postoperative laryngoscopy, a recommendation of the International Neural Monitoring Study Group. Neural stimulation at the end of surgery and postoperative function are highly correlated but not perfect.

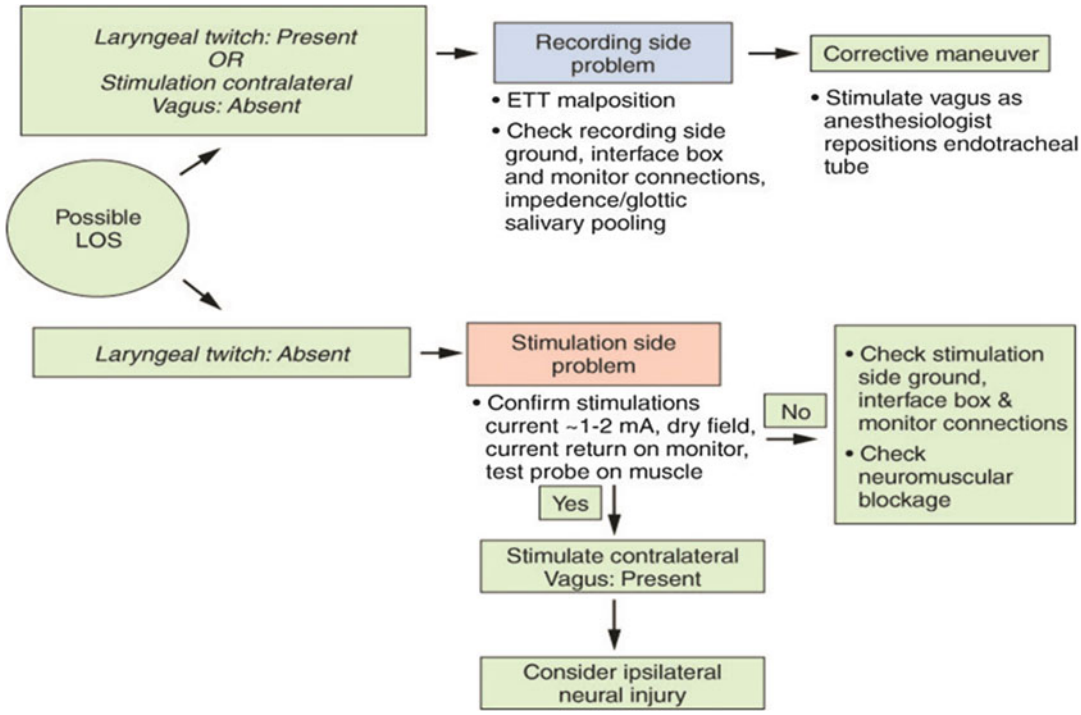

Fig. 36.4 IONM algorithm

Presurgical dissection and postsurgical dissection suprathreshold vagal nerve stimulation have been recommended to respectively verify the IONM system function to have confidence in its accuracy and for testing of the neural circuit after the dissection. The vagal stimulation after the dissection would prevent potential false-negative findings of stimulating a compromised RLN distal to the injury site. It may be uncertain in a focused parathyroid dissection if this would require a larger incision to gain access to the carotid sheath to perform this maneuver. The comfort level of the surgeon to gain this access through limited exposure may be quite variable from surgeon to surgeon when performing parathyroid surgery. This would be an interesting area for future study.

Anesthesia

Standards in anesthesia have been provided by the International Neural Monitoring Study Group [18]. Muscle relaxation should be avoided because the monitoring would be sensitive to neuromuscular blockade. This blockade is avoided during the induction of general endotracheal anesthesia, or if it is necessary during induction, a short-acting agent is needed [20, 26]. Careful and open dialogue with the anesthesia team is necessary for this coordinated team effort.

Equipment

Various methods have been developed to monitor RLN and SLN activity. The vast majority of experiences have examined intermittent RLN monitoring using a probe to stimulate anatomic structures of concern. Continuous stimulation has been described and is discussed later in the chapter under future direction. The most commonly used strategy employs an electromyographic (EMG) system utilizing a specialized endotracheal tube with surface electrodes to monitor activated laryngeal musculature secondary to stimuli including pressure, heat, traction, or intentional stimulation with a probe

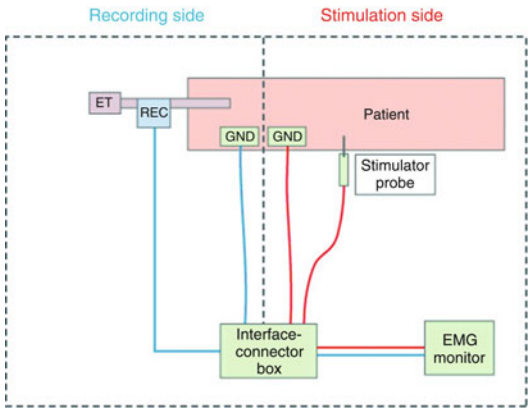

Fig. 36.5 Basic monitoring equipment setup

[20]. Commercial availability and ease of use have made endotracheal tubes with surface electrodes as sensors for RLN monitoring very popular. As previously stated, this would be of no value for those parathyroid surgical cases performed under local anesthesia. Another technique that has been used but requires greater skill, experience, and general anesthesia is the placement of hook electrodes, intramuscular vocal cord electrodes [4, 27]. Finally, postcricoid surface electrodes have been found effective but not used in widespread fashion [28]. General equipment setup including the algorithm for monitoring tube placement intubation, recording and stimulation ground electrodes, patient positioning and tube fixation, and monitor setting (Fig. 36.5) have been well described by International Neural Monitoring Study Group [18], and the International Guidelines Statement serves as an excellent reference.

Contemporary Trends and Future Direction

Although a preponderance of data fails to show that neuromonitoring significantly reduces the rate of nerve injury in thyroid and parathyroid surgery, surgeons seem to be increasingly using the technology [20]. The potential benefits of nerve identification, dissection, prediction of nerve injuries, and reduction in the risk of bilateral RLN injury have been outlined. Surveys have delved into the thought process of surgeons as to why they use IONM. One of the most recent studies was a multi-institutional survey of 103 otolaryngology and affiliated 103 general surgery programs in the United States evaluating trends in intraoperative neural monitoring for thyroid and parathyroid surgery. A majority of otolaryngologists, 80.6 %, and 48 % of general surgeons reported using IONM. Use in all cases was 44.3 % for otolaryngologists and 30.8 % for general surgeons. High-volume surgeons tended to use IONM more. The study results indicated that general surgeons tended to use IONM for RLN identification, and otolaryngologists tended to use it more for dissection, resection, and medicolegal consideration purposes. There appeared to be a discordance in motivation for its use [29].

Finally, preliminary studies are exploring the dynamic assessment of the nerve through continuous vagal monitoring. This could be advantageous to alert the physician regarding EMG changes that may herald an impending nerve injury and allow for modification of surgical maneuvers to reverse the situation [30, 31]. Future studies will be needed to provide data regarding the impact of this strategy on surgical outcomes, particularly as it applies to parathyroid surgery.

Summary

Intraoperative nerve monitoring has been extensively studied in thyroid and parathyroid surgery, but much of the literature has focused primarily on its role in thyroid surgery. Contemporary parathyroid surgery with often a more directed and minimal approach may not necessarily warrant the routine use of IONM for those surgeons who perform this procedure under a general anesthetic. However, there are circumstances in parathyroid surgery where the use of IONM may be very valuable and the knowledge gained from its routine use by a surgeon in endocrine surgery can be of utmost value in those cases. Reoperative parathyroid surgeries, glands adherent to the nerve, ectopic or missing glands, nonlocalizing glands, and patient anatomic constraints will con-

tinue to create challenges in the future for surgeons and the use of IONM as a surgical adjunct can prove very helpful despite a lack of literature evidence that it prevents nerve injuries.

Society Guidelines
International Neural Monitoring Study Group and the International Guidelines Statement [18].

Best Practices: N/A

Expert Opinion
Understanding the value and limitations of intraoperative nerve monitoring as an adjunct in parathyroid surgery is essential for optimization of surgical outcomes specific to the unique circumstances of parathyroid gland surgery. Continued study and development of IONM will refine well-established guidelines that serve as a current template for its use.

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Outpatient Parathyroidectomy

37

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Contents

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Introduction

Most cases of primary hyperparathyroidism are caused by a single parathyroid adenoma. Minimally invasive parathyroidectomy for parathyroid adenomas can be performed in the outpatient setting; patients are typically discharged from the recovery room within hours after surgery if they meet discharge criteria. This chapter reviews the concept of outpatient parathyroidectomy, optimal preoperative localization algorithms, patient selection criteria, technical surgical aspects, and safety and outcomes of outpatient parathyroidectomy.

Primary Hyperparathyroidism

Primary hyperparathyroidism is most commonly caused by adenomatous transformation of the parathyroid glands, with involvement of a single gland in the vast majority of cases (>80 %), while a minority of patients are affected by multigland disease [1–3]. Several gene abnormalities have been implicated in the tumorigenesis of parathyroid glands. The relocation of cyclin D1/PRAD1 proto-oncogene in juxtaposition to the 5′-PTH gene sequence is established as a major contributor to the development of up to 40 % of sporadic parathyroid adenomas [4–6]. PRAD1 encodes cyclin D1, which is a major cell cycle regulator

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that controls the transition from G1 to S phase of the cell cycle. In transgenic mice models, parathyroid-targeted over-expression of cyclin D1 has resulted in excessive proliferation of parathyroid cells [7]. The menin tumor suppressor gene has a role in the development of multiple endocrine neoplasia syndrome (MEN) type 1, as well as some sporadic primary hyperparathyroidism cases [8]. Some studies have suggested that somatic mutation and/or deletion of both menin alleles are implicated in more than 20 % of sporadic parathyroid tumors [8]. There also are several other familial forms of primary hyperparathyroidism, including MEN syndromes type 2A, familial primary hyperparathyroidism, and hyperparathyroidism-jaw tumor syndrome. Understanding the etiology of primary hyperparathyroidism is important in careful patient selection for minimally invasive parathyroidectomy in the outpatient setting.

Preoperative Localization

The concept of minimally invasive and outpatient parathyroidectomy is predicated on accurate preoperative localization of enlarged parathyroid glands [9, 10]. There are different imaging modalities that can be employed for this purpose. It is critical that surgeons understand the advantages and disadvantages of each localization technique, as well as the sensitivity of each respective imaging modality at their own institution, in order to choose the best and most pertinent imaging algorithm.

Ultrasound

Cervical ultrasound often is used to identify enlarged parathyroid glands. Sonographically, parathyroid adenomas typically appear as round to ovoid lesions with lower echogenicity than thyroid tissue (Fig. 37.1). A feeding extrathyroidal vessel may be seen entering at one pole [11]. Neck ultrasound for the detection of parathyroid adenomas has a reported sensitivity of 72–89 % and is operator dependent [11, 12]. Advantages of using ultrasound as a localizing study include portability of the machine, potentially making it an office procedure, avoidance of ionizing radiation, overall low costs, and the ability to identify coexisting thyroid pathology. Ultrasound is less useful in patients with significant obesity, large goiters, and those with ectopic, very posteriorly or retrosternally positioned parathyroid adenomas.

Sestamibi Scintigraphy

Sestamibi (six methoxyisobutylisonitrile) is a monovalent lipophilic cation that diffuses passively across cell membranes and concentrates in the mitochondria. Hyperfunctional parathyroid glands have a rich supply of mitochondria that concentrate sestamibi [13]. Sestamibi scans are obtained following injection of ^{99m}Tc-sestamibi and then again approximately 2 h later, in order to identify foci of retained radiotracer activity after thyroid gland washout [14]. Residual signal usually indicates parathyroid hyperfunction [15] (Fig. 37.2). Sestamibi scanning alone has a sensi-

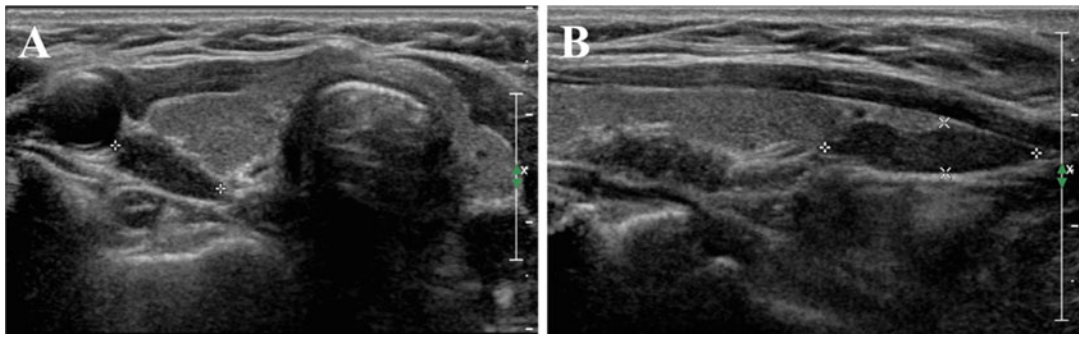

Fig. 37.1 Cervical ultrasound demonstrating a right inferior parathyroid adenoma (**a**) Transverse view; (**b**) Longitudinal view

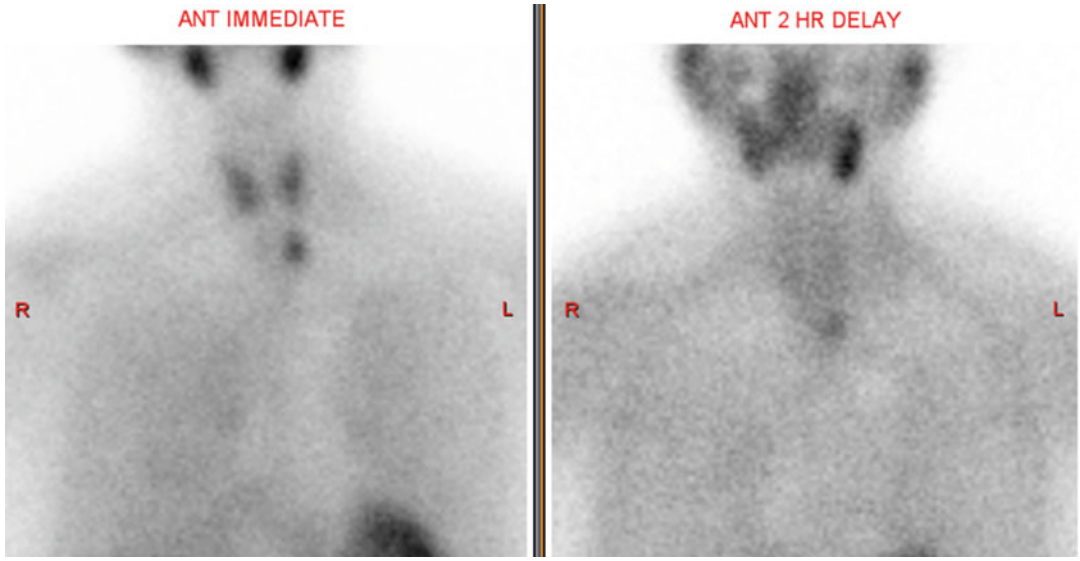

Fig. 37.2 Sestamibi scan following injection of 99mTc-sestamibi, and then again approximately 2 h later; a focus of retained radiotracer activity is seen after thyroid gland washout in the left inferior position denotes a left infrathyroidal parathyroid adenoma

tivity of 60–80 % [16]. Sestamibi scanning is less accurate in patients with very small parathyroid adenomas, parathyroid hyperplasia, and concurrent inflammatory or neoplastic thyroid disease. Nevertheless, sestamibi scintingraphy may be advantageous in patients with ectopic or supernumerary parathyroid tumors. Excessively "hot" parathyroid sestamibi scans may preoperatively suggest a diagnosis of parathyroid carcinoma.

Sestamibi-Single Photon Emission Computed Tomography (Sestamibi-SPECT)

Sestamibi-SPECT is a three-dimensional sestamibi scan that integrates the functional form of sestamibi imaging with the surrounding anatomic structures identified by a computed tomography scan, improving the accuracy of sestamibi scanning (Fig. 37.3). In a large prospective series of 338 patients who underwent sestamibi-SPECT for primary hyperparathyroidism, the overall sensitivity of sestamibi-SPECT was 82 %, but sensitivity varied greatly with the number and pathology of affected parathyroid glands; the technique correctly identified 90 % of solitary adenomas, 73 % of double adenomas, and 45 % of multigland hyperplasia [17]. Sestamibi-SPECT appears to be more accurate and superior to sestamibi scan alone for localization of parathyroid adenomas.

Four-Dimensional Computed Tomography (4D-CT)

4D-CT is a four-phase CT technique that offers additional information with regard to the perfusion status of potential parathyroid lesions by assessing the dynamic contrast enhancement properties of the candidate lesions [11] (Fig. 37.4). A noncontrasted phase is performed first. Iodinated contrast is then administered, and examination is performed at different intervals from the time of injection (arterial phase). Subsequent images are obtained at 30 and 60 s (washout phase). Identification of parathyroid adenomas using this technique is based on the fact that adenomas are characterized by rapid uptake and washout of contrast. Typically, parathyroid adenomas have initial low density, rapid increase in density to 60 s, followed by rapid washout of contrast [11]. 4D-CT is a promising

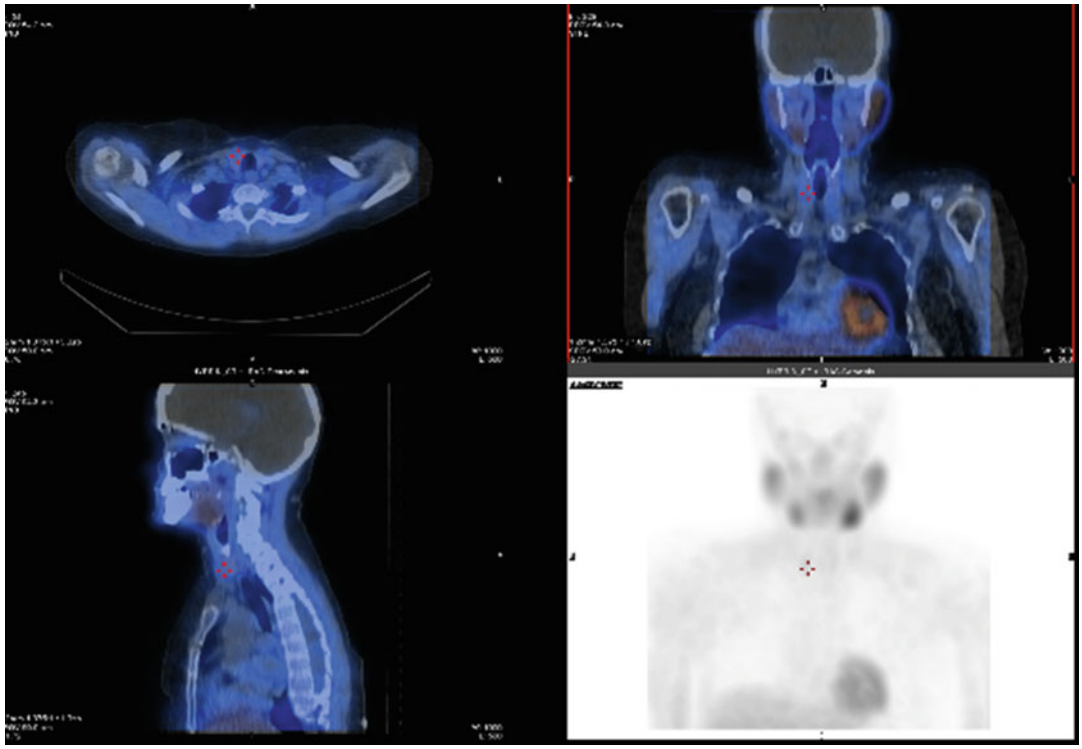

Fig. 37.3 Sestamibi with SPECT scan with superimposed images of three planes screen capture demonstrating a right-sided parathyroid adenoma

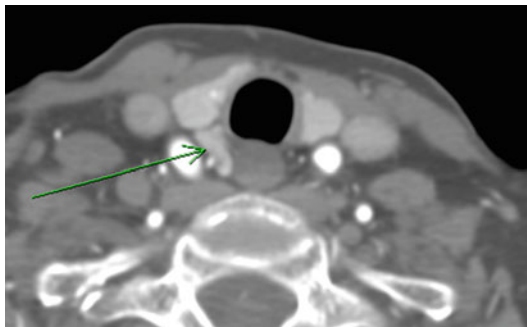

Fig. 37.4 4D-CT scan demonstrating a right inferior parathyroid adenoma

technique for preoperative parathyroid localization, with improved accuracy. The reported sensitivity of 4D-CT for single-gland disease is as high as 94 % [18]. The addition of 4D-CT to previously negative or inconclusive ultrasound and sestamibi-SPECT is often advantageous, with a reported sensitivity of 71.8 % [12]. The major disadvantages of 4D-CT are the higher radiation exposure associated with the technique, which is of particular concerns in young patients, and the need for iodinated intravenous contrast administration. Patients with severe allergy to contrast and those with renal insufficiency may not be candidates for 4D-CT.

Magnetic Resonance Imaging (MRI)

While MRI is an acceptable localization technique for parathyroid tumors, its utility in localizing enlarged parathyroid glands is limited by the considerable overlap between the appearance of parathyroid tissue, lymph nodes, and exophytic thyroid tissue. Parathyroid adenomas appear hypointense on T1 images and hyperintense on T2 images (Fig. 37.5). Sensitivity of MRI for enlarged parathyroid glands ranges from 43 to 82 % [19, 20]. MRI is seldom used as a primary localization imaging technique in primary hyperparathyroidism. However, it may be considered a reasonable

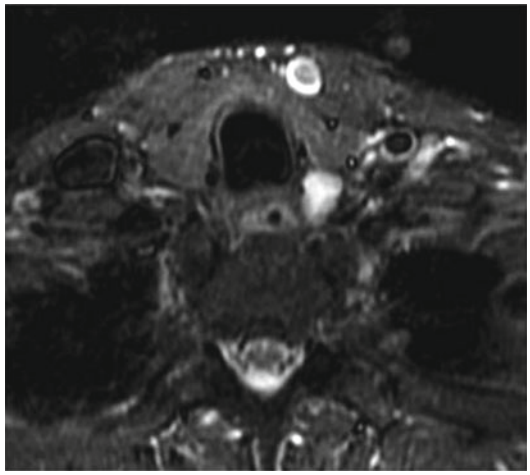

Fig. 37.5 MRI of the neck demonstrating hyperintense uptake in a left-sided parathyroid adenoma on T2-weighted imaging

second-line localization test for pregnant patients with primary hyperparathyroidism if a cervical ultrasound is nonlocalizing, as it offers cross-sectional imaging without radiation exposure.

Algorithm for Preoperative Localization

Good preoperative localization of an abnormal parathyroid gland is necessary for undertaking outpatient parathyroidectomy. Surgeons should employ the various imaging studies based on the probability of accurate localization at their own institution.

In a decision tree analysis, Wang et al. examined the cost-utility of various preoperative imaging algorithms before undergoing initial parathyroidectomy for sporadic primary hyperparathyroidism—based on sensitivity and cost-effectiveness of individual imaging studies. Patients were randomized to one of five preoperative localization protocols: (1) ultrasound; (2) sestamibi-SPECT; (3) 4D-CT; (4) sestamibi-SPECT and ultrasound; and (5) sestamibi-SPECT and ultrasound and 4D-CT, if discordant (sestamibi-SPECT and ultrasound ± 4D-CT). Ultrasound was the least expensive, followed by 4D-CT; sestamibi-SPECT and ultrasound ± 4D-CT; sestamibi-SPECT; and sestamibi-SPECT and ultrasound. Sestamibi-SPECT and ultrasound ± 4D-CT were most cost-effective because of improved localization resulting in fewer bilateral surgical neck explorations. Compared to sestamibi-SPECT, ultrasound, 4D-CT, and sestamibi-SPECT and ultrasound ± 4D-CT resulted in a win–win situation costing less because of the enhanced ability to perform limited, outpatient parathyroidectomy. Based on this analysis, a cost-effective imaging algorithm can be developed for preoperative localization of parathyroid adenomas, in which cervical ultrasound should be used first. If the ultrasound is indeterminate, then a combination of 4D-CT and/or sestamibi-SPECT should be employed [21]. While we believe that this algorithm is efficient and effective in localizing abnormal parathyroid adenomas for outpatient parathyroidectomy, it is important to recognize the need for individualization in certain conditions. For example, use of 4D-CT may not be appropriate in the setting of patients with renal insufficiency or in those with significant contrast allergy. Also, 4D-CT may not be easily available at many institutions; therefore, imaging algorithms need to be optimized based on best available studies.

Outpatient Parathyroidectomy

Surgery is the only curative treatment strategy for primary hyperparathyroidism. Parathyroidectomy is recommended for all patients with biochemically proven disease who have symptoms involving target organs, such as nephrolithiasis, severe bone disease, pancreatitis, peptic ulcer disease, and severe neurocognitive dysfunction [22, 23]. In the United States, the overwhelming majority of patients with primary hyperparathyroidism exhibit nonspecific symptoms that cannot always be easily attributed to primary hyperparathyroidism. These nonspecific symptoms include fatigue, weakness, headaches, anxiety, mental depression, and reduced neurocognitive function, such as "mental cloudiness." Traditionally, patients presenting with these nonspecific findings were considered "asymptomatic." However, it is reasonable to argue that the term "asymptomatic" may be a misnomer [23].

According to the Fourth International Workshop on Asymptomatic Primary Hyperparathyroidism guidelines, parathyroidectomy is indicated in asymptomatic primary hyperparathyroidism patients who are younger than 50 years, with a serum calcium level of 1 mg/dL above the normal limit, glomerular filtration rate of less than 60 mL/min, or bone density at the hip, lumbar spine, or distal radius that is more than 2.5 standard deviations below peak bone mass. Nephrolithiasis, nephrocalcinosis, or radiographic evidence of vertebral fracture are clear indications for parathyroidectomy (Table 37.1) [22].

Traditional parathyroidectomy dictates a bilateral neck exploration, with identification of all parathyroid glands, even for patients with single-gland disease. This approach proves to be effective, with cure in over 97 % of cases, when the operation is performed by experienced surgeons [10, 24]. However, a large majority of patients with primary hyperparathyroidism harbor a single abnormal parathyroid gland, prompting the concept of unilateral, or focused neck exploration if the location of the abnormal gland can be identified preoperatively. Improvements in accuracy of preoperative localization techniques coupled with the successful introduction of intraoperative rapid PTH monitoring have obviated the need for bilateral neck exploration in most cases and led to the successful development of minimally invasive parathyroidectomy or parathyroidectomy via unilateral/focused neck exploration. Currently, minimally invasive parathyroidectomy is an established approach for parathyroidectomy and has become the standard of care in the hands of experienced parathyroid surgeons for the management of sporadic primary hyperparathyroidism [10]. Published data have established that minimally invasive parathyroidectomy is equally effective to the bilateral neck exploration technique in curing primary hyperparathyroidism [9, 10, 25].

Historically, patients undergoing parathyroid surgery via bilateral neck exploration stayed in the hospital for 1–2 days. Successful implementation of minimally invasive or focused parathyroidectomy has challenged the need for such inpatient admission or even an extended overnight/23-h observation patient stay. This has

Table 37.1 The Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism (2013) and the Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism (2008) guidelines for surgical management of asymptomatic primary hyperparathyroidism patients

Criterion	2008[a]	2013[b]
Patient age (years)	<50	<50
Serum calcium (> normal limit)	1 mg/dL	1 mg/dL
BMD *T*-score[c]	< −2.5 at any site	< −2.5[d]
Fracture	Previous fragility fracture	Vertebral[e]
Creatinine clearance	<60 cc/min	<60 cc/min
24-h urinary calcium	–	>400 mg/day and increased stone risk[f]
Nephrolithiasis/nephrocalcinosis	–	Yes[g]

BMD bone mineral density, *CT* computed tomography, *MRI* magnetic resonance imaging, *VFA* vertebral fracture assessment

Data adapted from:

[a]Bilezikian JP, Khan AA, Potts JT Jr; Third International Workshop on the Management of Asymptomatic Primary Hyperthyroidism. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. *J Clin Endocrinol Metab*. 2009; 94:335–9

[b]Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab.* 2014; 99:3561–3569

[c]Z-scores, instead, for premenopausal women and men younger than 50 years

[d]At lumbar spine, total hip, femoral neck, or distal 1/3 radius

[e]Any radiographic evidence of vertebral fracture (CT, MRI, or VFA)

[f]Increased stone risk by biochemical stone risk analysis

[g]Evidence of nephrolithiasis or nephrocalcinosis (X-ray, ultrasound, or CT)

led to parathyroidectomy becoming truly outpatient surgery, where patients are discharged within hours after successful completion of the operation if meeting discharge criteria.

Patient Selection

In general, patients with single-gland parathyroid adenomas are considered to be the best candidates for outpatient parathyroidectomy. Patients with indeterminate preoperative parathyroid localization studies, multigland disease, familial primary hyperparathyroidism, multiple endocrine neoplasia type 1 or 2A, poorly localized recurrent disease, suspected parathyroid carcinoma, or those who are considered for concurrent total thyroidectomy may not be candidates for the procedure, given the potential for higher likelihood of having postoperative complications and requiring serial laboratory calcium checks or aggressive calcium supplementation in the immediate postoperative period [9, 24].

Choice of Anesthesia

Outpatient parathyroidectomy can be performed under superficial regional cervical block with sedation, or general anesthesia with endotracheal intubation or laryngeal mask.

The superficial cervical block should be complemented by intravenous sedation with fentanyl and/or midazolam in order to minimize patient anxiety, while maintaining consciousness of the patient such that the patient can phonate upon request to allow the surgical team to assess the integrity of the recurrent laryngeal nerve. The superficial cervical block is performed by the surgeon after the patient has been positioned and mild sedation has been administered by the anesthesiologist. Usually, 10 cc of 1 % lidocaine with/out epinephrine (1:100,000) is administered (1) posterior and deep to the ipsilateral sternocleidomastoid muscle at Erb's point (Fig. 37.6a); (2) along the entire anterior border of the ipsilateral sternocleidomastoid muscle (Fig. 37.6b); and then (3) using a combination of 1 % lidocaine with/out epinephrine mixed with 0.5 % marcaine in a 1:1 ratio along the anterior line of the neck incision in the dermis and under the platysma (Fig. 37.6c). Care should be taken not inject the local analgesic agent intravascularly [9]. Before proceeding to injecting analgesic to the contralateral side, one must assess the patient's voice and cough, thereby assuring that the ipsilateral vagus nerve or phrenic nerve have not been anesthetized inadvertently. If the cervical block inadvertently involves both vagus nerves, bilateral vocal cord paresis and breathing problems can result, and this potential airway emergency should be avoided at all costs. Certainly, bilateral cervical blocks can be performed to facilitate bilateral exploration, but great caution should be employed to intermittently assess the integrity of recurrent laryngeal nerve function and the patient's airway.

Data have demonstrated that superficial cervical block may provide significant advantages with regard to the immediate postoperative recovery. In a study of 177 consecutive primary

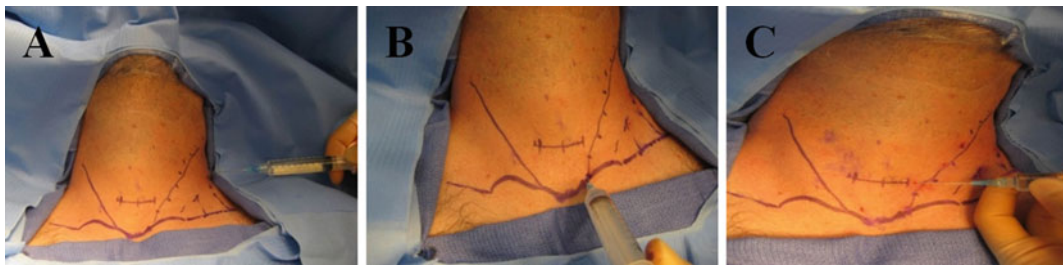

Fig. 37.6 Superficial cervical block for outpatient parathyroidectomy. 10 cc of 1 % lidocaine is administered (**a**) posterior and deep to the ipsilateral sternocleidomastoid muscle at Erb's point; (**b**) along the entire anterior border of the ipsilateral sternocleidomastoid muscle; (**c**) a combination of 1 % lidocaine mixed with 0.5 % bupivicaine in a 1:1 ratio injected along the anterior line of the neck incision in the dermis and under the platysma muscle

hyperparathyroidism patients who underwent minimally invasive parathyroidectomy, patients who experienced surgery under cervical block (41 %) vs. general anesthesia had better pain control, required less narcotic pain medications, and were less likely to experience nausea or vomiting postoperatively [26]. Surgeon-performed superficial cervical block with monitored sedation/anesthetic care is effective and advantageous in the setting of outpatient parathyroidectomy for well-suited patients, such as those who are motivated, with normal thyroid glands or small goiters, and who have no significant contraindications to sedation (such as severe chronic obstructive pulmonary disease). General anesthesia is an acceptable alternative for outpatient parathyroidectomy for patients who do not fit criteria for superficial cervical block with sedation.

Operative Technique

Before commencement of surgery, preparation for adequate blood draws for intraoperative rapid PTH monitoring should be done. A large intravenous line (16–18 gauge) is inserted in an adequate forearm vein. A blood pressure cuff can be placed on the ipsilateral arm above the intravenous line and inflated when blood draws are desired for PTH monitoring, thereby acting as a tourniquet. Arterial line placement for blood draws is most often unnecessary. A first, baseline intraoperative rapid PTH level should be obtained prior to the skin incision. The patient is placed in the "beach chair" neck extension position (or "sniffing position"), and the neck is prepped and draped. Sedation and the surgeon-performed superficial cervical block are then undertaken as described above. A 2–4 cm Kocher midline incision in a natural skin crease is performed, allowing access to both sides of the neck if that should become necessary during the procedure.

A focused, ipsilateral exploration is then undertaken based on the preoperative imaging studies. The strap muscles are divided in the midline raphe, and the thyroid is medially retracted to allow visualization of the paratracheal area. The culprit parathyroid gland is found and carefully dissected out, assuring that its capsule is not violated, thus avoiding any risk of implantation of parathyroid cells in the neck; its vascular supply is clipped or ligated, and the parathyroid adenoma should be removed intact. The ipsilateral recurrent laryngeal nerve must be protected and preserved. Once the parathyroid gland is resected, intraoperative rapid PTH samples are drawn by the anesthesia team via the intravenous line, at time 0 min post-resection, and every 5 min thereafter for a total of 15 min. The patient's incision can be closed while waiting for the intraoperative PTH results. The procedure is concluded if the PTH drops by 50–65 % from the baseline PTH levels into the normal range, usually within 10–15 min after removal of the hyperfunctioning parathyroid gland [22]. Older patients may have longer PTH half-lives; therefore, additional samples may need to be drawn. The 50 % drop in serum PTH levels into the normal range is a reliable test for documentation of successful identification and resection of the offending parathyroid glands; however, a more aggressive drop of >60–65 % has been proposed recently to improve the rate of missed multigland disease [27–32]. The patient is then observed in the recovery room for a few of hours to assure they do not have nausea or neck swelling suggestive of an expanding hematoma.

Same-Day Discharge Criteria

Patients may be discharged on the same day as surgery if the following criteria are met: successful completion of minimally invasive parathyroidectomy with the ability to ambulate, void and tolerate oral fluids without nausea; the patient's pain is controlled well with oral agents; the incision is flat without evidence of bleeding or evolving hematoma; the voice is intact; and the appropriate social situation for discharge exists. Discharge education should include detailed diet, activity, medication, and follow-up instructions. Specific symptoms and signs of rapid hematoma formation and possible postoperative hypocalcemia should be explained, along with clear instructions for contacting the surgeon's office or team with any problems or questions [9, 10]. Good and timely communication

between the patient and the surgical health care team is important in the immediate postoperative period.

Outcomes

While postoperative hemorrhage is rare after parathyroid surgery, it is a major concern after outpatient parathyroidectomy, given the potential for airway obstruction and the need for immediate surgical attention. In a study of 4140 patients who predominantly underwent outpatient thyroidectomy and parathyroidectomy at a high-volume institution, cervical hematoma occurred in just 18 patients (0.43 %), including one patient (0.13 %) who had parathyroidectomy. Of all patients who developed postoperative cervical hematomas, 39 % were on anti-platelet therapy. With regard to timing of presentation of the cervical hematomas, 28 % occurred within hours in the recovery room, 11 % in <6 h, 39 % in 6–23 h, and 22 % in >24 h. All hematomas associated with airway compromise occurred in the recovery room, whereas hematoma presentation after that timeframe did not require emergent bedside decompression [33]. Therefore, preoperative evaluation and identification of patients at increased risk of bleeding is important; this includes patients with bleeding disorders or those receiving anti-platelet/anticoagulation therapy. These patients require rigorous technical attention and may need planned overnight/23 h observation periods.

Published evidence has demonstrated that parathyroidectomy for patients with localized single-gland primary hyperparathyroidism can be performed safely in the outpatient setting, with superior short-term outcomes and equivalent long-term cure and recurrence rates, as compared to bilateral neck exploration [10, 24, 34–36]. In a large study from the University Health System Consortium, Stack et al. analyzed data from 21,057 cases of outpatient parathyroidectomy and 13,434 cases of inpatient parathyroidectomy. Compared to inpatient parathyroidectomy, outpatient parathyroid surgery was associated with a lower incidence of hypocalcemia (0.28 % vs. 4.05 %) and overall complications (0.29 % vs. 5.24 %), as well as reduced hospital charges ($12,738 and $14,657) [35]. On the other hand, earlier data suggest that minimally invasive parathyroidectomy may be associated with a small increase in risk of long-term recurrence. Schneider et al. compared outcomes between minimally invasive parathyroidectomy ($n=928$) versus routine parathyroidectomy ($n=155$) in 1083 patients with single parathyroid adenomas. They found that minimally invasive parathyroidectomy was equivalent to routine surgery for both disease persistence and recurrence overall (2.7 % vs. 1.9 %, respectively, $p=0.58$). When the authors analyzed recurrence over time, they observed a nonsignificant trend toward greater long-term recurrences ($p=0.55$) in the minimally invasive group beyond 8 years of follow-up [37]. It is important to point out that interpretation of this finding was limited by the few recurrence events in the study that precluded multivariable adjustment. To address this issue, the same group conducted a larger follow-up study in which they reexamined the impact of minimally invasive parathyroidectomy compared to routine bilateral parathyroid surgery on outcomes in a multivariable fashion. The study included 1006 cases of minimally invasive parathyroidectomy and 380 cases of routine bilateral parathyroid surgery. In adjusted time-to-event analysis, a minimally invasive approach compared to bilateral parathyroidectomy was not associated with increased risk of disease recurrence ($p=0.34$) [34]. This compelling finding suggests strongly that the long-term outcomes of minimally invasive and routine bilateral parathyroidectomy are equivalent. Thus, outpatient parathyroidectomy is an effective approach for patients with well-localized parathyroid disease.

Special Considerations

Elderly Patients

Primary hyperparathyroidism is more common in the elderly, a population that is often affected by multiple comorbidities and severe manifestations of hyperparathyroidism. In the past, surgeons were less likely to operate on many elderly patients due to the perceived higher risk of postoperative complications from patient

comorbidities and general anesthesia, as well as the lack of certainty of symptomatic benefit from the procedure [38]. Published data from high-volume surgeons have demonstrated that parathyroidectomy in elderly patients is safe, curative, and beneficial [38]. However, Thomas et al. demonstrated that in a multi-institutional cohort study of more than 7000 patients elderly patients undergoing parathyroidectomy sustained more morbidity following parathyroidectomy than a younger cohort. They concluded that advanced age may be an independent risk factor worth considering in surgical decision-making [39].

Outpatient parathyroidectomy has now been extended to elderly patients with primary hyperparathyroidism at high volume centers [40, 41]. Shin et al. evaluated the safety and efficacy of outpatient parathyroidectomy in 101 elderly patients who were ≥70 years, compared to 287 patients younger than 70 years. Although the elderly cohort had higher preoperative serum creatinine and PTH levels, more severe osteoporosis, and more compromised bone density scores, the rates of postoperative complications were similar between the elderly and younger patient groups (5.9 % vs. 3.5 %, respectively, $p=0.38$). The vast majority of elderly patients (78 %) were successfully discharged on the same day of surgery. They concluded that minimally invasive parathyroidectomy can be performed as safely in the elderly as in younger patients [41].

While outpatient parathyroidectomy for elderly patients may be advantageous in reducing risks of hospital-associated complications such as infections and delirium, appropriate preoperative medical evaluation and patient selection is important in this potentially vulnerable population.

Morbid Obesity

Outpatient parathyroidectomy is more challenging in morbidly obese patients. Certain intraoperative concerns may require planning and coordination with the anesthesia team, particularly with regard to optimal positioning of the patient and the choice of anesthesia. Superficial cervical block may not be appropriate for morbidly obese patients, because of coexistent conditions that can be exacerbated while in the supine position, such as back pain and obstructive sleep apnea, which may often necessitate endotracheal intubation [42].

Technically, the operation is more difficult in the setting of morbid obesity, requiring longer cervical incisions and more extensive operative time [43].

Published data suggest that morbidly obese patients undergoing parathyroidectomy have significantly longer operative times and a higher likelihood of experiencing postoperative wound complications [44]. In a study that examined the impact of morbid obesity in the setting of outpatient parathyroidectomy, morbidly obese patients were more likely to require endotracheal intubation, longer cervical incision, and extended observation time in the recovery room; however, all morbidly obese patients were still discharged on the same day, and without complications [43]. These data demonstrate the safety of outpatient parathyroidectomy in morbidly obese patients; however, it is critical to emphasize the importance of the coordinated and collaborative surgeon and anesthesia team experience in achieving superior outcomes from the procedure, as these data represent experiences from high-volume centers.

Summary

For the majority of patients with primary hyperparathyroidism, parathyroidectomy can be performed in the outpatient setting for patients who undergo focused exploration, where the patients are discharged from the recovery room within hours after surgery. Outpatient parathyroid surgery for well-localized parathyroid adenomas is superior to traditional parathyroidectomy, with a lower incidence of hypocalcemia, overall complications, and costs. Outpatient parathyroidectomy is predicated on accurate preoperative localization of the offending parathyroid gland(s) and rapid intraoperative parathyroid hormone monitoring. The optimal algorithm for preoperative localization (depending on local availability)

may include cervical ultrasound first, followed by 4D-CT and/or Sestamibi-SPECT if the ultrasound is indeterminate in its findings. Outpatient parathyroidectomy may not be appropriate for patients with indeterminate preoperative localization studies, multigland disease, familial primary hyperparathyroidism, multiple endocrine neoplasia syndromes, suspected parathyroid carcinoma, and for those who require extensive bilateral neck exploration.

Society Guidelines

The most recent guidelines of the Fourth International Workshop on Asymptomatic Primary Hyperparathyroidism were published in 2014 [22, 45]. The workshop included recommendations regarding the surgical indications for parathyroidectomy, and established certain important maxims. Patients with primary hyperparathyroidism who meet surgical criteria should be referred to an experienced endocrine surgeon to discuss the risks, benefits, and potential complications of surgery. Patients who do not meet surgical criteria but for whom there are no contraindications to surgery may benefit from a consultation with an experienced parathyroid surgeon or should have their case reviewed in a multidisciplinary endocrine conference with surgeon involvement. Imaging is not a diagnostic procedure—it is a localization procedure to help the surgeon optimize the operative plan. Hereditary forms of primary hyperparathyroidism may be more prevalent than initially thought, and physicians should be mindful of these entities [46]. Surgery is likely to benefit most patients, given the high cure rates, low complication rates, and the likelihood of arresting and/or reversing existing bone disease [45].

The American Association of Endocrine Surgeons and the American Association of Clinical Endocrinologists Task Force is expected to publish revised guidelines for the surgical management of primary hyperparathyroidism in the near future.

Best Practices

Patients with primary hyperparathyroidism may be more symptomatic than historically thought. Given the high cure rate of surgery when performed by experienced surgeons, all patients with primary hyperparathyroidism should be referred for surgical consultation with an experienced surgeon to determine the risks and benefits of parathyroidectomy. Preoperative radiographic imaging can enhance the ability to identify parathyroid adenomas, and thus improve the likelihood of having the patient undergo minimally invasive parathyroidectomy. Outpatient parathyroidectomy for well-localized parathyroid neoplasia performed by an experienced surgeon is superior to traditional parathyroidectomy, given a lower rate of associated complications, reduced costs, and a similarly high cure rate and low long-term recurrence. Therefore, outpatient parathyroidectomy should be considered for primary hyperparathyroidism patients who meet criteria.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion

Outpatient minimally invasive parathyroidectomy performed by experienced surgeons for appropriately chosen patients is superior to traditional bilateral neck exploration, with the benefits of faster recovery, lower complication rate, reduced costs, and equivalent long-term cure. Preoperative localization imaging studies should be carefully chosen in order to enhance the ability of the patient to undergo minimally invasive surgery; this means that surgeons need to be aware of their own institutional sensitivity and specificity for radiologic studies, and may need to use a combination of studies to allow better identification of parathyroid adenomas. With the increasing focus on value-based surgical care, experienced parathyroid surgeons should consider outpatient parathyroidectomy for patients who meet criteria for minimally invasive exploration and same day discharge.

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Neurocognitive Symptoms and Hyperparathyroidism

38

Michael C. Singer

Contents

Introduction

Classically, patients with primary hyperparathyroidism (PHPT) presented with overt features of the disease, such as pathologic fractures or severe nephrolithiasis. Clinicians do not debate the value of intervention in these patients and they are as a matter of course referred for surgery.

However, with the introduction of more sensitive laboratory technology and widespread screening, patients with PHPT are now being identified earlier in the course of their disease. Consequently, the majority of patients now being diagnosed do not have clear disease sequelae. However, many do complain of more nebulous symptoms, such as fatigue, depression, emotional lability, memory deficits, and a feeling of "walking around in a cloud." Uncertainty exists about the value of surgery in "asymptomatic" PHPT. The National Institute of Health guidelines delineate indications for surgery in these patients [1]. As with previous iterations, in the most recent guidelines, published in 2014, neurocognitive symptoms were not included as an indication for surgery. Explaining the omission, the authors cite the lack of clear, convincing evidence that neurocognitive problems are associated with PHPT and can be reversed with surgery.

Yet these recommendations conflict with the experience of many clinicians involved with the care of "asymptomatic" PHPT patients.

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Anecdotally, many patients do complain of neurocognitive symptoms prior to surgery and some percentage do report marked improvement afterwards. Research assessing the association between hyperparathyroidism and neurocognitive symptoms and the impact of surgery has provided mixed results to this point.

Pathophysiology

The etiology of the neurocognitive symptoms that can occur in PHPT is unclear. Hypercalcemia may be the cause, as calcium is a known regulator of neurotransmitter function. Additionally, it has been suggested that calcium may have a direct or indirect impact on cerebral function [2]. At the same time, a number of studies have suggested that parathyroid hormone itself may play a role in the development of neurocognitive symptoms. As with calcium, this potentially is due to a direct effect on cerebral processing or through indirect mechanisms, such as impairment of cerebral vasculature function [3, 4]. The influence of calcium and PTH on brain function may be the cause of changes in functional imaging of the brain that have been demonstrated in patients with PHPT before and after surgery [5].

However, teasing apart the precise cause of the vague neurocognitive symptoms often seen in patients with hyperparathyroidism can be difficult for several reasons. Comorbidities can often result in the same symptoms. Many patients with PHPT are older and these patients may have a number of potential concurrent causes of neurocognitive changes. Additionally, vitamin D deficiency, frequently present in patients with PHPT, can also lead to vague systemic complaints. These confounding factors likely contribute to the lack of clear, consistent data relating parathyroid disease and neurocognitive difficulties and the potential impact of parathyroidectomy.

Evidence of Association

Patients can experience both psychiatric and cognitive symptoms in PHPT. Psychiatric features can include depression (ranging from dysthymia to frank depression), anxiety, emotional lability, irritability, and sleep disturbances. Cognitive symptoms are often more vague in their presentation. They can include complaints of feeling hazy, poor concentration, difficulties with learning, and memory impairment.

Psychiatric Symptoms

There are a large number of studies looking at the possible association between hyperparathyroidism and psychiatric symptoms. Most of these have been case series or case control studies with limited numbers of patients [6, 7]. There are also three prospective, randomized trials (RCT) that have examined the link between quality of life (QOL) and PHPT. These three studies included psychiatric elements in their QOL assessments.

Many studies have demonstrated that when compared with the general population, patients with PHPT appear to more commonly experience vague psychological (and cognitive) symptoms. Additionally, several studies have found that the majority of PHPT patients report marked subjective improvement in their symptoms after surgery [8–10]. Interestingly, some percentage of patients only appear to recognize after successful surgery the degree that symptoms were present preoperatively [11]. Unfortunately, while these studies may document improvements in nonspecific psychological symptoms after surgery, most do not utilize validated surveys or instruments designed to objectively document specific abnormalities. As a result, the strength of their findings is debatable.

Two recent, relatively large case-control studies investigated the association specifically between depression and PHPT. Patients undergoing parathyroidectomy were compared to both those who were observed and other patients who had thyroid surgery. Both of these studies utilized scales (the Hospital Anxiety and Depression Scale and Patient Health Questionnaire-9) specifically developed to assess depression and anxiety [7, 12]. Parathyroidectomy was shown in both groups to significantly reduce depressive symptoms. Suicidal ideation was also reduced in the group undergoing surgery.

Scale	Hospital Anxiety and Depression Scale	The Short Form 36 Health Survey (SF-36)	The Symptom Checklist-90-R (SCL-90-R)	Comprehensive Psychopathological Rating Scale (CPRS)
Number of items	14 items	36 items	90 items	65 items
Sections	– Anxiety – Depression	– Vitality – Physical function – Bodily pain – General health perception – Physical role function – Emotional role function – Social function – Mental health	– Somatization – Obsessive-compulsive – Interpersonal sensitivity – Depression – Anxiety – Hostility – Phobic anxiety – Paranoid ideation – Psychosis	
Time to complete	Brief, 2–5 min	Extended	12–15 min	50 min
Design	To detect anxiety and depression in patients with physical health problems	To assess overall health status	To evaluate a broad range of psychological problems	To assess treatment effects on wide range of psychological symptoms

The three RCTs on this subject conducted to date investigated the influence of parathyroidectomy on general and psychiatric QOL factors. In all three studies patients with "mild" PHPT were randomized to undergo surgery or be observed.

The study by Rao et al. from 2000 followed 53 patients for 2 years and QOL was measured by using the Short Form 36-Item (SF-36) Health Survey and the Symptom Checklist 90 (SCL-90R) scale [13, 14]. Interestingly, this trial demonstrated no difference in baseline SF-36 scores between PHPT patients and normal subjects. Patients who underwent surgery demonstrated a significant improvement in social functioning and emotional role function and a reduction in anxiety and phobia.

In 2007, Ambrogini et al. reported on their trial that included 50 patients [15]. As with the Rao et al. study, before the intervention no differences existed between the patients in regard to QOL measurements. However, at 6 and 12 months after surgery significant improvements were reported in general health, vitality, mental health, and bodily pain. No change was found in social functioning and emotional role function after surgery in this study.

The largest of the three trials included 191 patients with PHPT who did not meet 2002 National Institute of Health criteria for surgery [16]. In contrast with the two other RCTs, in this trial, when compared to a matched population who did not have hyperparathyroidism, PHPT participants had lower SF-36 scores and more psychological symptoms on the Comprehensive Psychopathological Rating Scale. However, 2 years after surgery, the intervention cohort did not exhibit a clear improvement in these measures compared to the observation group.

Cognitive Manifestations

Many of the studies that have revealed an improvement in nonspecific psychiatric symptoms after parathyroidectomy also document a positive impact on vague cognitive complaints. But only a limited number of studies have tried to examine the impact of hyperparathyroidism

and parathyroidectomy on cognitive abilities specifically. These utilize formal, validated cognitive research instruments. As with the psychiatric focused research, the results of these studies have been inconsistent. This is likely partially due to limited number of patients, lack of controls, and variations in the specific aspects of cognition tested. One other muddling element is that psychiatric symptoms are known to impact cognitive abilities. It is possible that the psychiatric symptoms present in these patients may be confounding the results of the cognitive testing.

In 2005, Roman et al. reported on a prospective study which used a number of validated psychometric and neurocognitive instruments to determine the impact of surgery on learning, memory, and concentration [17]. Patients undergoing parathyroidectomy were matched with those having thyroid surgery. After surgery, the parathyroidectomy patients demonstrated significant improvement in spatial learning. Other cognitive measures did not show a difference.

Babinska et al. also specifically examined the cognitive impact of parathyroidectomy in a prospective, case-control study [18]. Prior to surgery, the 35 PHPT patients demonstrated significantly decreased concentration levels, nonverbal learning processes, use of constructional and visual memory, and verbal resources. Postoperatively, there were significant improvements in visual memory, visual-constructive abilities, and direct memory.

The only RCT that focused particularly on cognition was a small study, which included only 18 patients [19]. In addition to formal neuropsychological testing, brain function was assessed using functional magnetic resonance imaging (fMRI). Sleep fitness was also measured. While differences were found in sleepiness, no significant change in the cognitive scales was identified between those undergoing surgery and those who were observed.

Summary

To date, the preponderance of studies investigating the association between hyperparathyroidism and neurocognitive symptoms demonstrates that these features are more prevalent among PHPT patients. Additionally, most of these have found that surgery appears to reduce the severity of these symptoms, whether psychiatric or cognitive. These findings are consistent with the experience of many clinicians who treat patients with PHPT.

However, the results of studies on this topic are far from universal or invariable. Even among the RCTs that have focused on this topic the findings are quite mixed and sometimes even contradictory.

Given the lack of clear evidence of an association between hyperparathyroidism and neurocognitive symptoms, it is not surprising that there is no available research that provides predictive information on the impact of surgery for patients. No study for example suggests calcium or PTH levels above or below which surgery can be expected to impact these symptoms. Without this, clinicians cannot provide any accurate guidance to patients regarding who might benefit from surgery and which symptoms and to what degree they might improve.

While it does appear that there is a link between neurocognitive symptoms and hyperparathyroidism, the lack of larger, rigorous studies designed with consistent methodologies, which employ validated, specific measures, has prevented this connection from being more fully elucidated. In the future, additional, well-designed RCTs are needed to clarify this association.

Society Guidelines

Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99(10): 3561-9.

Best Practices N/A

Expert Opinion

The results of studies examining the association between hyperparathyroidism and neurocognitive symptoms are too inconsistent at this time to reach clear conclusions. As a result, physicians should not consider these symptoms as an adequate criteria for surgery. Patients can reasonably be advised that surgery in some patients might lead to improvement in these types of symptoms. However, no assurances should be given to any individual patient.

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39 Health Services and Health Care Economics Related to Hyperparathyroidism and Parathyroid Surgery

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Contents

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Introduction

Chronic diseases are modifiable, increasingly prevalent, and costly. An aging population and an evolving system for the delivery of health care have helped to focus attention on the economic burden of chronic illness. From the resources devoted to the care of those with chronic illnesses, including the 300 billion dollar spending total by Medicare in 2010, to the productivity lost because of absence from the workplace, these diseases place a significant financial strain on the US population and the economy [1, 2].

Hyperparathyroidism (HPT) is the third most common chronic endocrine disorder, behind diabetes mellitus and hyperthyroidism [3]. It is estimated that 25 new cases per every 100,000 people will be diagnosed annually in Western countries, with a progressively increasing incidence felt to be a result of wider access to care, ease of screening, and ability to track and detect metabolic abnormalities as a result of the electronic health record [4–6]. Enthusiasm for preventive care practices, championed by government health authorities, corporations with large employee health insurance plans, and the medical community alike, will likely fuel the trend toward screening of asymptomatic populations [7–10]. The rise in obesity, with its attendant renal complications, may also precipitate a steady stream of people being diagnosed with secondary parathyroid disease.

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Moreover, the increasing development and implementation of radiographic techniques may identify subpopulations of patients with incidentallydiscovered anatomic parathyroid abnormalities. These developments highlight the likelihood that parathyroid pathology will continue to be identified with increasing incidence [5].

The rising incidence of primary hyperparathyroidism (PHPT) carries with it an economic burden. With one out of every 1000 individuals found to have PHPT, financial considerations include those associated with diagnostic evaluation, therapy, and short- and long-term sequelae of untreated disease. Standard of care in the workup of HPT includes a serum metabolic panel, as well as serum intact parathyroid hormone (PTH) and vitamin D levels, at a minimum [4]. With some frequency, referring physicians are following this basic laboratory workup with imaging, albeit premature in the primary care setting, which is occasionally inconclusive and often expensive [6, 11]. Following diagnosis, decisions regarding necessity and mode of management have cost implications. The variety of management strategies and costs associated with them is underscored by the number of cost-effectiveness analyses published that seek to inform health care providers and other decision makers regarding the fiscally responsible care of their patients [12–17]. If undiagnosed or untreated, however, myriad sequelae can manifest in the natural course of PHPT, which ultimately predispose toward greater health care costs [3, 4, 18–21]. Acute hypercalcemia in the short-term, as well as decreased bone mineral density, cardiovascular disease, renal dysfunction, and psychological disturbance in the long term, and an association with various non-parathyroid cancers, all lead to greater expenses in untreated parathyroid disease [18, 19, 22–24]. Clearly, the economic burden of HPT, treated or untreated, contributes to the growing cost of US health care.

Epidemiology

A recent study of 12 years of electronic health record data, including 2.7 million US patients, suggests that in spite of widespread screening practices, there is a lag in the time from first documentation of hypercalcemia to diagnosis of PHPT, indicating that perhaps the current prevalence of the disease is underestimated [6]. Of the known patient population, though, PHPT is typically diagnosed in the fifth through seventh decades [5, 25]. Women are approximately twice as likely as men to develop PHPT in populations younger than 45 years old, although this ratio balances out to almost 1:1 after 45 years of age [3, 4, 6, 25]. In one study, incidence was greatest in individuals of black race, an often underserved community with socioeconomic barriers impeding access to care in the USA, suggesting that initial presentation in this race cohort may occur with more severe symptoms and require more resources, expeditious treatment, and ultimately greater strain on the US health care system [26–29].

PHPT is the most common cause of hypercalcemia in the outpatient setting, with 20 % of hypercalcemic patients presenting in US emergency departments subsequently diagnosed with PHPT [5, 22]. In contemporary series, only approximately 5–11 % of individuals present with symptoms. This is in contrast to the proportion of patients with symptoms at initial presentation prior to 1974 when screening became common practice [3, 5, 30]. Even when not presenting acutely, those with PHPT tend to have worse overall health, and poorer quality of life and workplace productivity, thereby increasing the economic toll of chronic HPT [31–33].

A review of the MarketScan database reflects the current state of PHPT demographics in the USA. This database is an integrated compilation of longitudinal data collected from more than 180 million unique patients over the past 20 years, bringing together information from inpatient, outpatient, laboratory, and pharma sources [34]. We undertook a retrospective observational cohort study of all patients diagnosed with PHPT, using International Classification of Disease, 9th Revision (ICD-9) codes for HPT(252.00, 252.01, 252.02, 252.08 and 259.3), as well as Current Procedural Terminology (CPT) codes for parathyroidectomy (60500, 60502, 60505, and 60512), in order to obtain demographic and treatment data in this US cohort from years 2009 to

2011. Individuals were included if they were enrolled with an insurance plan for at least 360 days prior to, and 360 days following, the first date in which one of these ICD-9 or CPT codes was documented. This review excluded data on individuals younger than 18 years of age and those with documented evidence of chronic kidney disease, identified by ICD-9 codes (585.1, 585.2, 585.3, 585.4, 585.5, 585.6, and 585.9), as we sought to identify only patients with PHPT.

Our final sample ($N=31,825$) corroborates demographic findings from previous epidemiologic research [3, 5, 25]. We found the median age for individuals with documented PHPT was 53 years. In our sample of patients over 18 years old, females ($N=23,994$) outnumbered males ($N=7831$) three to one in documented PHPT diagnoses. Given its consistency with published statistics, our cohort was further studied to identify trends in management, as later described.

Costs of Management

Medical Versus Surgical Management

There has been much discussion regarding appropriate management of patients in the era of widespread screening, as the majority of patients are asymptomatic at diagnosis [27, 35]. Certainly, definitive therapy for PHPT is surgical [30, 36]. There is evidence that even in patients who continue to be asymptomatic for years of active monitoring, decrements in overall health are observed by 15 years following diagnosis [15]. As an example, loss of bone mineral density has been observed even in patients without overt symptoms [20, 23]. In an analysis of an employer claims database and the Medicare Standard Analytic files, costs related to osteoporosis and the consequent non-vertebral fractures are not only strains on the health care system but also a significant cause of lost productivity [37]. Additionally, quality of life after parathyroidectomy has been shown to substantially improve, even among patients initially thought to be asymptomatic by current diagnostic guidelines, with corresponding improvement in workplace absenteeism [38–40]. Hence, definitive treatment, when indicated and patient-appropriate, appears to enable significant cost savings over time.

Using our MarketScan cohort, we studied the current status of PHPT therapy in the USA. Surgical management, as indicated by claims for CPT codes 60500, 60502, 60505, and 60512, was documented for 24.2% ($N=7687$) within a year of the date in which the first diagnostic claim for PHPT was made. In this subset of PHPT patients, the median interval from first documentation of PHPT in the claims database to parathyroid surgery was 44 days, with 83.5% ($N=6418$) of procedures performed in an outpatient setting. As such, most individuals had a length of stay less than 24 h. A search through outpatient pharmaceutical claims was undertaken to attempt to identify symptomatic patients (i.e., with indication for surgical intervention) who were otherwise unfit for surgery. No statistically significant differences in use of calcimimetics, bisphosphonates, or other medications used for PHPT treatment were found between nonsurgical and surgical patients. Specifically, cinacalcet hydrochloride was used by 0.3% of nonsurgical patients and 0.5% of surgical patients ($p=0.079$). Alendronate sodium was used by 3.8 and 3.5%, respectively ($p=0.325$). Zoledronic acid was used by 0.1 and 0%, respectively ($p=0.094$). No other medication comparison reached statistical significance when comparing nonsurgical PHPT patients with PHPT patients who underwent parathyroidectomy. This finding underscores the emphasis placed on surgical management, as well as the advances in technique that have made parathyroidectomy accessible to a more morbid population, making pharmacologic nonsurgical management an uncommon practice in PHPT patients with a surgical indication.

Several analyses comparing costs related to management of PHPT have substantiated the economic advantage of parathyroidectomy relative to medical observation and therapy. When considering a short time frame, surveillance with or without pharmacologic treatment appears to be less costly then surgical intervention given the greater up-front expense of surgery. However,

because PHPT is a lifelong disorder without surgery, the long-term costs of medical therapy and follow-up make parathyroidectomy the more cost-effective option when considering a longer time frame. It deserves mention that financial considerations are not only dependent on time frame but also on perspective, a nuance recognized particularly among those familiar with cost-effectiveness analyses (CEA) [41]. Discrete perspectives include, but are not limited to, those of the patient, the provider, the third-party payer, and society in general. While these perspectives may not all be mutually exclusive, they significantly change the costs considered in the management of a disease process.

Despite variation in the design of contemporary studies addressing costs of PHPT, surgical intervention is consistently shown to be more cost-effective than nonoperative management, even for asymptomatic patients [15, 16, 21]. Sejean et al. [24] analyzed the cost-effectiveness of three surgical approaches, as well as nonoperative surveillance, for a hypothetical 55-year-old asymptomatic female, using a health care delivery perspective. In their Markov model, three different surgical strategies and a strategy of medical management were compared over a lifetime horizon with a 1-month cycle. Across a reasonable range of associated costs, surgery remained more cost-effective than monitoring, except when there was no decrement in a medically managed patient's quality of life [16, 24]. Zanocco et al. [15] found that in a hypothetical 60-year-old asymptomatic patient fit for surgery, using a third-party payer perspective, the incremental cost-effectiveness ratio (ICER) for parathyroidectomy was $4778 (2005 USD) per quality-adjusted life-year (QALY) gained, well below the commonly used threshold of $50,000–100,000 USD per QALY [16, 41, 42]. Pharmacologic therapy was not cost-effective, with an ICER significantly greater than $50,000 (2005 USD) per QALY, when calculating costs over the lifetime of an asymptomatic patient. Therefore, in an asymptomatic population, given a life expectancy greater than 5 years, even without costs of medications, annual follow-up may be less costly but is less effective than surgical treatment [13, 15, 24].

Current recommendations suggest that patients younger than 50 years of age, regardless of presence of symptoms, should always be referred for surgery on the basis of their expected remaining lifespan, provided they are otherwise fit for surgery [36, 43]. Zanocco and Sturgeon [13] compared cost-effectiveness of parathyroidectomy, observation, and pharmacologic management in an asymptomatic patient, varying the patient life expectancy from 0.5 to 75 years. Using a third-party payer perspective, they found that observation was preferable to inpatient parathyroidectomy if life expectancy was less than 6 years. Otherwise, parathyroidectomy should be pursued as the most cost-effective option. This threshold changed, however, when comparing surgery in an outpatient setting to observation and pharmacologic therapy. Observation was more cost-effective than parathyroidectomy only if life-expectancy was less than 4.5 years. Outpatient surgery became the preferable strategy with anticipated life-expectancy greater than 4.5 years. Pharmacologic therapy, with an ICER ranging from $2.5 to $10.5 million (2005 USD), was dominated by any other strategy [13].

Therefore, in an asymptomatic patient, the available evidence suggests that observation is less costly but less effective, and thereby less cost-effective, than parathyroidectomy. This changes only for patients with an anticipated life expectancy less than 4.5 years since this was the threshold determined for surgery performed in an outpatient setting, which is the most common practice currently [44–46]. Pharmacologic therapy without surgery is less effective and more costly for patients with asymptomatic PHPT.

Surgical Approach

In patients with symptoms who are fit for surgery, parathyroidectomy is invariably indicated and cost-effective. While there is no debate regarding use of surgical intervention in this patient population, there is considerable variation in surgical approach and use of preoperative localization studies, with a correspondingly large variation in studies addressing costs associated with these practices [14, 16, 17, 24, 47–51].

A number of surgical approaches to parathyroidectomy are employed depending on disease localization, confidence in preoperative imaging, and surgeon preference. Bilateral, or four-gland, neck exploration (BNE) was standard of care prior to the implementation of many of the now-common localization studies and minimally invasive surgical techniques. With these newer technologies has come a shift toward limited exploration (LE), which encompasses one-gland focused exploration, two-gland unilateral exploration (UNE), and minimally invasive parathyroidectomy (MIP) approaches [44, 52]. A recent survey of surgeons performing parathyroidectomies revealed that only 10 % are still using BNE as their initial approach [44]. The practice of initial BNE is supported by its 95 % success rate consistently observed in the hands of experienced parathyroid surgeons, thereby limiting costs associated with recurrence or persistence of disease [11, 49, 53]. However, initial BNE without preoperative localization studies has greater probability of incurring costs related to complications, given the extent of surgical exposure placing more anatomical structures at risk of injury. Additionally, LE tends to have fewer costs associated with operating room time and postoperative length of stay, as many patients undergoing LE are able to avoid inpatient admission [14, 44]. Ultimately, the arguments pertaining to surgical approach and need for localization studies stem from concern regarding occult multi-glandular disease and failure of surgery to achieve a postoperative normo-hormonal and normo-calcemic state [11, 54].

Review of cost-effectiveness analyses studying the surgical approaches to parathyroidectomy reveals a lack of consistency in findings regarding the most successful, and therefore the most cost-effective, technique. Using a third-party payer perspective and probabilities based on success and complication rates of a cohort of patients at a tertiary care hospital, Baliski et al. [47] performed a decision analysis of UNE with preoperative localization sestamibi scan, BNE without preoperative localization, and MIP with preoperative localization scan, comparing cost-effectiveness in terms of avoiding complications. They found that UNE was more costly and less effective than BNE with an ICER of $5065 (2006 Canadian) per complication avoided. They found that MIP was slightly more effective than BNE in terms of avoiding complications but cost nearly $30,000 (2006 Canadian) per complication avoided, a sum they deemed prohibitive. BNE remained the most cost-effective option up to a societal willingness-to-pay threshold of $5000 (2006 Canadian) per complication avoided [47]. Because LE necessitates preoperative localization imaging and its associated costs, Baliski et al. found that BNE is the most cost-effective surgical approach when effectiveness is measured in terms of avoidance of surgical complications. However, the validity of this conclusion for a US population is uncertain since the authors note that a short time horizon was used, with probabilities based on small sample sizes, and complications only including symptomatic hypocalcemia and paresthesia . Hence, questions of cost-effectiveness among surgical approaches for PHPT remained unresolved without further corroborative studies.

Using an asymptomatic PHPT patient population and a health care delivery perspective, Sejean et al. [24] also compared the cost-effectiveness of three surgical approaches, as well as nonoperative surveillance as previously noted. In this Markov model, comparisons were made between BNE under general anesthesia without preoperative localization study performed, UNE under local anesthesia with preoperative ultrasound and sestamibi scan in addition to intraoperative PTH measurement, and video-assisted endoscopic parathyroidectomy (VAP) under general anesthesia with preoperative ultrasound and sestamibi scan in addition to intraoperative PTH measurement. Their model measured effectiveness in terms of QALYs, using a 1-month cycle length and a lifetime horizon. With these parameters, they found that a strategy of VAP was slightly more cost-effective than both UNE and BNE with an ICER of €17,250 (2002 Euros) per QALY. The ICER of UNE relative to BNE was €2688 (2002 Euros) per QALY. However, UNE became more cost-effective than VAP when the patient was older than 71 years of age, owing to the mortality risk associated with general anesthesia at this age threshold, or when only ultrasound without further

imaging was used preoperatively to localize the pathologic gland. Provided that localization techniques are conclusive and concordant, they show that a focused approach is generally more cost-effective than BNE when specifically attempting to maximize QALYs, rather than to minimize complications as in Baliski et al. [24, 47].

Ruda et al. [51] also undertook a cost-effectiveness comparison of LE and BNE. Unlike Sejean et al. [24] however, they used the perspective of the health care provider and defined effectiveness as postoperative normocalcemia. Ruda, Stack, and Hollenbeak designed a decision analysis comparing BNE without preoperative localization to minimally invasive radioguided parathyroidectomy (MIRP) following initial sestamibi scan, without further imaging as long as results from this initial scan were conclusive. If initial scan results were inconclusive, a subsequent ultrasound was performed, followed by UNE. Base-case analysis revealed that pursuing initial sestamibi scan was not only less costly but more effective than BNE without localization, with an ICER of −$28,505 (2001 USD) per additional patient effectively treated. The sestamibi strategy was dominant over a reasonable range of probabilities and costs for scanning and operative strategies [51].

Because of the variation in perspectives, definitions of effectiveness, and costs assigned to different therapeutic strategies, uniformity is lacking between the available cost-effectiveness analyses addressing surgical approach, and conclusions are not easily generalizable. One's definition of success, either achievement of surgical cure or avoidance of surgical complications, would suggest different strategies in the surgical management of a PHPT patient according to the above analyses. Further study is needed to corroborate these findings and guide surgeons in the efficient and high value care of their patients.

Preoperative Gland Localization

Approximately 85 % of patients with PHPT are found to have a solitary adenoma precipitating PTH excess. In these cases, resection of just one gland potentially provides surgical cure. Therefore, LE has become an increasingly common practice [44]. Patient evaluation prior to LE often includes one or more localization study to direct focused exploration, with high-resolution ultrasound and radionuclide Tc-99m sestamibi scans being the most common studies obtained [12, 25, 44, 51]. When localization techniques are conclusive and concordant preoperatively, focused parathyroidectomy has cure rates comparable to BNE in contemporary surgical series [14, 49, 53]. Yet even among surgeons practicing a focused approach, there has been no standardization of practice in selection of localization studies, intraoperative adjuncts, and specific surgical technique [52, 55].

Pursuit of preoperative and intraoperative studies increases success rates when performing LE, but concomitantly increases costs. The full complement of localization techniques include ultrasound, sestamibi scanning, sestamibi-single photon emission computerized tomography (sestamibi-SPECT), computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and selective venous sampling, with the latter more often used in the re-operant neck [36].

Assuming most surgeons now elect to perform LE with preoperative localization, comparison of localization techniques is warranted given the variety in practice among surgeons [44, 48]. Wang et al. [56] performed a cost-utility analysis using a societal perspective to study the most cost-effective preoperative imaging algorithm: sestamibi-SPECT, ultrasound, 4D-CT, and combinations of these techniques. If the study was positive, patients underwent MIP; if it was negative, they either underwent BNE or further imaging. Wang et al. found that ultrasound, 4D-CT, sestamibi and a combination of the three studies were all more cost-effective than sestamibi-SPECT alone, with incremental cost utility ratios (ICUR) of −$221,303, −$30,907, and −$2952 (2010 USD) per QALY gained, respectively. Additionally, they found that the combination of all three techniques, if initial sestamibi and ultrasound were discordant, was still more cost-effective than BNE without localization.

If presented with inconclusive or discordant results on initial localization studies, surgeons must decide the next step in their evaluation and treatment plan, aware that costs continue to accumulate with more studies. Ruda et al. [50] performed a cost-effectiveness analysis to study the situation of negative findings on initial sestamibi scan, comparing strategies of additional imaging with preoperative ultrasound before LE, additional sestamibi-SPECT before LE, or BNE without further imaging. Using a health care provider perspective and defining effectiveness as postoperative normocalcemia, they determined that additional imaging with ultrasound was more effective and less costly than sestamibi-SPECT, generating an ICER of −$688,125 (2004 USD) per patient cured. Both preoperative adjuncts dominated BNE as they were both less costly and more effective in facilitating postoperative normocalcemia, with an ICER of $79,790 (2004 USD) per patient cured relative to sestamibi-SPECT.

Intraoperative Adjuncts

Most surgeons now supplement preoperative localization with intraoperative PTH (IoPTH) during LE because of concern regarding missed multi-glandular disease, even when preoperative localization studies are concordant [12, 14]. Because of concern regarding both false-positives and false-negatives using IoPTH, Agarwal et al. [17] compared the cost-effectiveness of IoPTH with obtaining same-day PTH and calcium measurements collected during MIP and available several hours postoperatively. Using a third-party payer perspective and defining effectiveness as resection of all pathologic parathyroid tissue, they found that in order to avoid a single failed MIP procedure and unnecessary conversion to BNE, same-day serum PTH and calcium measurements were the most cost-effective approach. This strategy had an ICER of less than −$19,000 (2001 Australian), thereby dominating IoPTH across a reasonable range of serum assay and hospital-bed costs. However, the generalizability of this study is uncertain since patients who undergo MIP tend not to have an inpatient admission, having been discharged before the opportunity to undergo laboratory evaluation postoperatively. Additionally, the authors admit to a significant selection bias in the patient population from which probabilities were derived since every patient met inclusion criteria for MIP. Given these concerns, uncertainty remains regarding the economic value of intraoperative adjuncts. The best use of these adjuncts appears to be in conjunction with localization techniques, in order to determine when MIP is appropriate, and in accordance with surgeon judgment, in order to determine when conversion to BNE is indicated intraoperatively.

Reoperation

Ongoing debate regarding surgical approach, choice of localization studies, and use of intraoperative adjuncts underscores concern regarding failure of parathyroidectomy to remove all pathologic parathyroid tissue [57, 58]. Siperstein et al. [48] conducted a prospective observational study to evaluate the efficacy of ultrasound, sestamibi, and IoPTH assay to guide a successful LE. They noted that surgical cure would have only been achieved using preoperative sestamibi in 70 %, ultrasound in 75 %, and both studies in 77 %. Even in situations of concordant scans as well as an appropriate drop in IoPTH during parathyroidectomy, occult multi-glandular disease would have been left in 16 % without BNE. Ruda et al. [12] found slightly more optimistic outcome data for the detection of a solitary adenoma, showing sensitivities of 88.44 % for sestamibi and 78.55 % for ultrasound. For multi-glandular disease, however, sensitivities plummeted to 44.46 and 54.86 %, respectively. While multi-glandular disease found by BNE does not necessarily equate with functional pathology, this study suggests that even in the most experienced hands, preoperative localization techniques are capable of false-negative results. Hence, surgeons must be cognizant that conversion to BNE remains an option even if pursuing LE initially, in order to avoid the costly outcome of failed surgery [48].

Certainly, failure to detect and resect pathologic parathyroid tissue represents the most costly outcome, as additional hospital, surgical, and radiologic costs are incurred for a second procedure, in addition to initial costs from the failed index procedure. The possibility of this outcome has prompted some surgeons, who may have been early proponents of LE to ultimately change their practice back to BNE [11]. Still, others persist with focused exploration even in patients requiring reoperation, provided adequacy of preoperative localization [58]. Since most missed lesions are found in eutopic locations, re-operant dissections tend to have altered planes, making identification and avoidance of important structures exceedingly difficult [59]. Fortunately, of the 7388 PHPT patients who underwent parathyroidectomy in the MarketScan data, only 8% ($N=592$) required reoperation within 90 days of their index procedure.

Nonoperative Management

Among the 100,000 new cases diagnosed annually, some patients will undergo nonsurgical follow-up. Although clinical indications for parathyroidectomy continue to evolve and are increasingly inclusive, a proportion of patients are either poor surgical candidates, have undergone first parathyroidectomy unsuccessfully and refuse further surgery, or refuse surgery initially [27, 30, 35, 36]. The available options for long-term medical management are limited to calcimimetics, estrogen replacement therapy for postmenopausal women, and bisphosphonates [32, 60]. As previously mentioned, when compared with parathyroidectomy, medical management has smaller up-front costs but is economically unappealing over one's lifetime, unless life expectancy is less than 4.5 years [13, 24, 61]. Over time, nonoperative surveillance may be associated with decreased bone mineral density, cardiovascular disease, renal dysfunction, and psychological disturbance, contributing to greater utilization of health care resources on a population level and greater medical expenses on an individual basis [23].

There is limited research regarding pharmacologic treatment of hypercalcemia in PHPT disease, with even fewer studies regarding costs in this patient population. Various studies, however, have assessed costs of pharmacologic treatment for hypercalcemia secondary to non-PHPT disease [61–65]. A review of cinacalcet, the only calcimimetic approved for use in humans, and its use in PHPT patients demonstrated that it is effective in controlling calcium and PTH levels, and that it may play a role in improving quality of life, but does not improve objective markers such as bone mineral density [32, 66, 67]. Cost-effectiveness of cinacalcet relative to other medical therapies in PHPT treatment is largely unknown as the majority of such analyses model costs using a secondary HPT model, a patient population in which dialysis is also commonly used [62–64, 68–74]. Bisphosphonates, antiresorptive medications frequently used for PHPT, often supplement cinacalcet in order to reverse the bone damage of PHPT. Again, analyses of cost data for medications used in PHPT are largely missing in the literature. The dearth of research studying medications for PHPT highlights the strength of the recommendation for surgery.

Summary

PHPT is a prevalent and costly disease. Because of increasingly inclusive indications for surgery, patients diagnosed with PHPT in the primary care setting are often referred for surgical evaluation. Significant variation in surgical practice exists, particularly as improved localization techniques and novel surgical approaches continue to evolve. Cost-effectiveness analyses have generally shown an economic advantage of surgery relative to nonsurgical management, in both symptomatic and asymptomatic individuals. Trends toward limited exploration are generally cost-effective relative to bilateral neck exploration, albeit with a correspondingly greater risk of missed occult multi-glandular disease and reoperation. This risk is balanced by the use of preoperative localization studies and intraoperative

parathormone assays, with costs that are additive although not prohibitive. Certainly, use of surgical adjuncts and choice of surgical approach are mediated by surgeon judgment, an unquantifiable factor in cost-effectiveness analyses. In spite of the multitude of studies addressing economic issues of PHPT, uniformity among conclusions drawn from these studies is lacking, in part because of the differences in study design. Further research is needed to prospectively validate findings among the currently published analyses and to define standard of care for clinicians.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion

Understanding the cost-effectiveness of treatment alternatives for patients with hyperparathyroidism, particularly regarding medical versus surgical approaches, the use of preoperative gland localization, and the use of intraoperative adjuncts, is important for providing care that optimizes outcomes for both patients and our health care system.

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Technologist's Perspective of Parathyroid Scintigraphy

40

Lorraine E. De Blanche, Tracy L. Yarbough, Isaac M. Filat, and Twyla B. Bartel

Contents

Introduction

The technologist plays a crucial role in parathyroid scintigraphy patient preparation and image acquisition. This chapter covers the physical parameters of image acquisition and variations that could be applied if the standard imaging protocol does not provide acceptable image quality. This chapter also includes a very short review of alternative radiopharmaceuticals and their protocols as well as brief statements on patient preparation.

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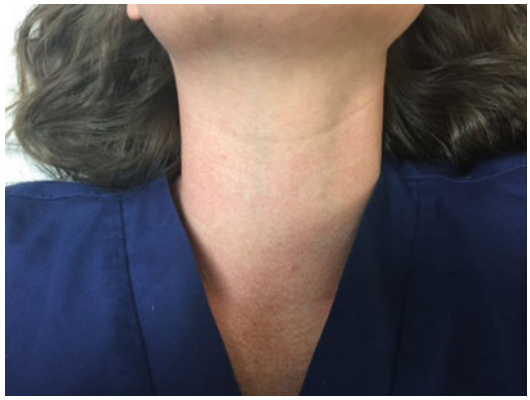

Fig. 40.1 It is important to examine the patient's neck for any masses or signs of prior surgery before the patient is imaged. Also, when imaging, the patient's chin should be up while the neck is extended as in this case

General Considerations Important to Technologist's Performance of the Procedure

Parathyroid scintigraphy is utilized to help guide the surgeon in the localization of a parathyroid adenoma(s), and thereby spare the patient from an extensive neck exploration. Preoperative localization helps shorten the surgical procedure time and reduce potential postsurgical complications 1].

In most cases, primary hyperparathyroidism is due to a single hyperfunctioning adenoma (80–85 %); hyperplasia is the cause in 12–15 % of cases, and parathyroid carcinoma in 1–3 % of cases [2, 3].

Documented pertinent clinical findings and laboratory results are extremely important. These include the serum calcium level, serum parathyroid hormone (PTH) level, and urinary calcium if available. Past history of thyroid disorders and prior surgery to the neck are also important to document. Inquiry should be made regarding any recent imaging with iodine-containing agents. Availability of any prior imaging can be very helpful. A quick physical evaluation of the neck by the technologist may also be useful (see Fig. 40.1). These factors will be a great help for the physician in interpretation of the images [4].

Several radiotracers or combinations of radiotracers and techniques, including subtraction imaging, have been utilized for this imaging procedure, but ^{99m}Tc-sestamibi is currently considered the international standard radiopharmaceutical as it is more accurate and less cumbersome than others. ^{99m}Tc-sestamibi localizes in both functioning parathyroid and thyroid tissue with the radiotracer washing out of normal thyroid tissue more rapidly than abnormal parathyroid tissue. SPECT-CT increases sensitivity and specificity, and aids in more precise anatomic localization of parathyroid adenomas [5]. For the sake of completeness, a short summary of alternative radiopharmaceuticals being used is discussed in a subsequent section of this chapter.

Indications

(a) Localization of a parathyroid adenoma(s) in patient with primary hyperparathyroidism or localization of any hyperfunctioning parathyroid tissue (hyperplasia). The clinical information of elevated calcium and parathyroid hormone can be very useful [5].
(b) Localization of any other type of hyperfunctioning parathyroid tissue (lower sensitivity in these cases).

Examination Time

- About 3 h if both of early and delayed images are acquired.
- About 45 min if only early images are obtained for presurgical purposes (per referring physician request).

Patient/Scan Preparation

1. No specific patient preparation is required EXCEPT THAT PATIENT MUST BE ABLE TO LIE VERY STILL DURING IMAGING. SEDATION MAY BE NEEDED FOR PATIENTS UNABLE TO REMAIN STILL.

Fig. 40.2 Example of a hot lab where the radiotracer is prepared

2. Some have suggested discontinuing calcium channel blockers prior to the procedure.
3. Documentation of elevated serum calcium and PTH levels, potential presence of concurrent thyroid disease, history of any prior thyroid or parathyroid surgery, prior administration of iodine-containing substances, and any other relevant imaging.

Radiopharmaceutical, Administered Activity, and Technique of Administration

- Radiopharmaceutical: ^{99m}Technetium-sestamibi.
- Administered activity: 20 mCi (740 MBq), range 10–35 mCi.
- Route of administration: Intravenous.

(See Figs. 40.2, 40.3, and 40.4 for examples of a hot lab, dose label, and lead pig.)

Equipment and Energy Windows (See Figs. 40.5 and 40.6)

- Camera: Large field-of-view dual-headed gamma camera.
- Collimator: Low-energy-high-resolution parallel hole.
- Energy window: 20 % Centered at 140 keV.

Patient Positioning and Imaging Field

- Patient position: Supine.
- Imaging field: Base of brain to inferior border of heart.

Acquisition Protocols and Acquisition Parameters [6]

- Wait for 15 min following radiopharmaceutical injection prior to imaging.
- At 15 min: High-count images are obtained in the planar projection in three views: LAO, RAO, and anterior collimation can be achieved by using a high-resolution parallel-hole collimator (a pinhole collimator can be used). If SPECT or SPECT-CT is unavailable, pinhole collimation is preferred. It is imperative to obtain images of the neck, including the parotid glands and extending caudally to at least the mid-myocardium. This protocol is especially helpful in recurrent hyperparathyroidism or patients with residual disease as the adenoma(s) occur most often in ectopic anatomical locations in these settings [7].

Planar Static Images

- Matrix: 128 × 128.
- Zoom: Zero.
- Acquire for 5 min in the ANT, R ANT OBLIQUE, and L ANT OBLIQUE projections.

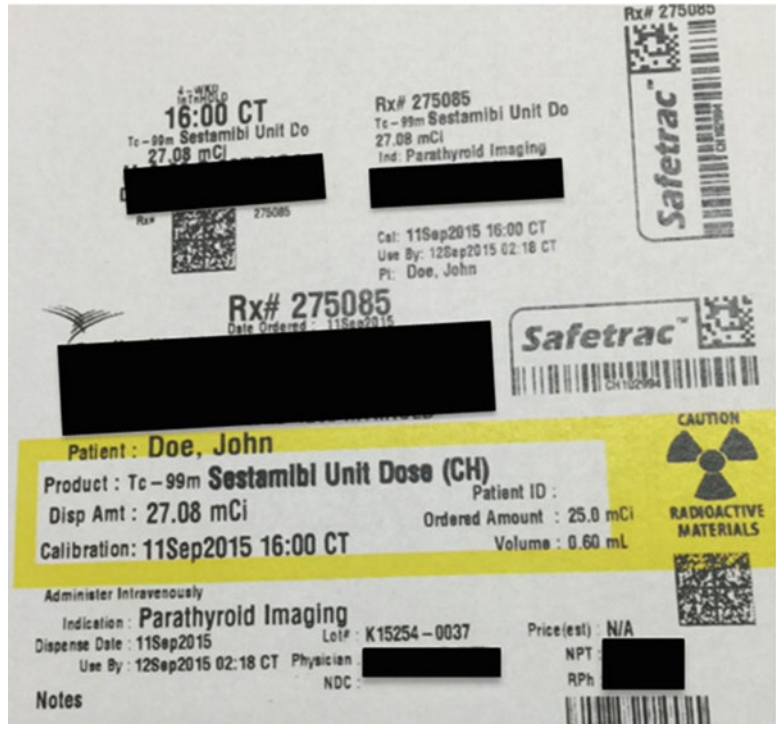

Fig. 40.3 Example of a label of a ^{99m}Tc-sestamibi dose (identifiers removed). Note that the dispensed dose, 27.08 mCi, is higher than the actual ordered or prescribed dose of 25.0 mCi. This discrepancy allows for interim decay of the radiotracer before the actual administration

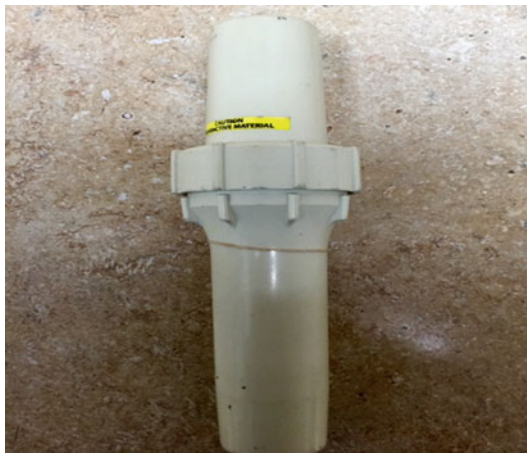

Fig. 40.4 The radiotracer to be injected is carried in a lead "pig" in order to prevent radiation exposure to surrounding patients and technologists

SPECT-CT Images: (See Table 40.1 and 40.2) [7]

- At 2 h, repeat 15-min protocol.
- An integrated SPECT-CT system is preferred, but the use of fusion software can produce images acquired on separate gamma cameras and CT scanners. In these instances, perfect alignment is crucial in obtaining adequate images for interpretation. The field of view must match that of the early images. The gamma camera should have large field of view with a high-resolution low-energy parallel-hole collimator.
- It is not necessary to obtain CT at both time points, as two SPECT sets and one CT are often adequate, thereby minimizing patient radiation dose. The SPECT data should be acquired over a 360^0 arc to optimally obtain 120 projections at 15–25 s per projection [8].

Data Processing [9]

- Planar: None.
- SPECT/CT: The exact procedure for processing SPECT images depends upon the computer software and camera being used. The reconstruction process in general terms is:
  1. OSEM/MLEM reconstruction with measured attenuation correction.

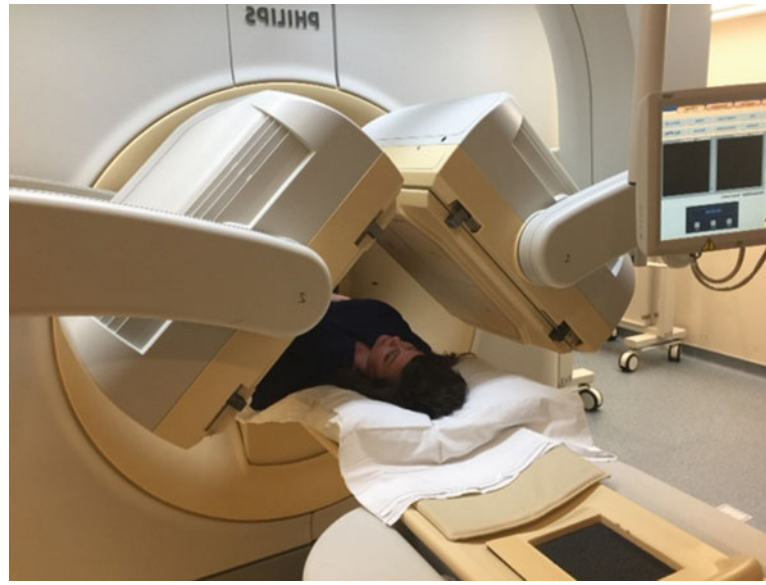

Fig. 40.5 Note that the patient is placed in the supine position with the gamma camera and CT aligned in order to scan from the level of the parotid gland to the mid-heart. This large field of view limits the possibility of missing ectopic parathyroid tissue

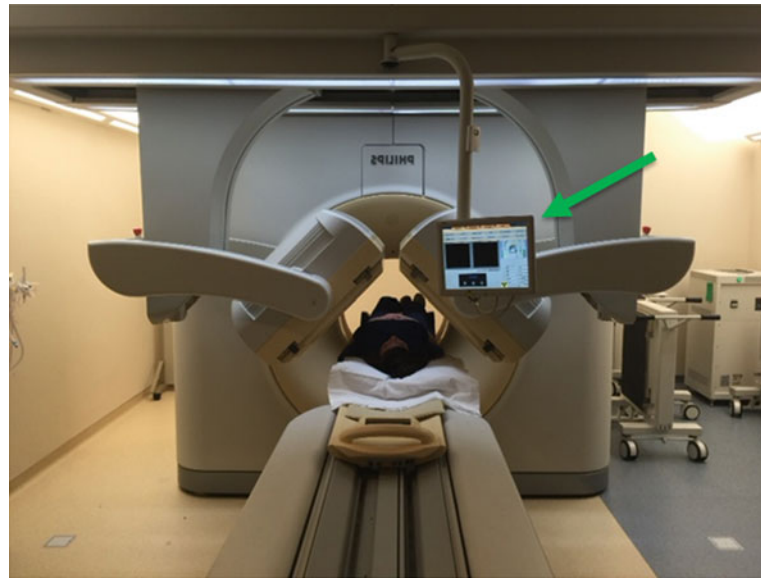

Fig. 40.6 Note the computer console to the right of the *arrow*. Parameters for the images are digitally entered into this console

Table 40.1 Sample parameters for correlative CT

Parameters	CT
Slice thickness	5 mm
Increment	5 mm
Number of scans	1
Rotation time	0.5 s
Pitch	0.9
Voltage	140 ke V
Current	20 mAs
Reconstruction matrix	512×512
Number of reconstructed slices	120

Table 40.2 Sample parameters for SPECT [10]

Starting angle*	0°	0°
Range	180° (each detector)	180° (each detector)
Number of stops	60	60
Method	Step and shoot	Step and shoot
Time/step	40 s 64×64	40 s 64×64

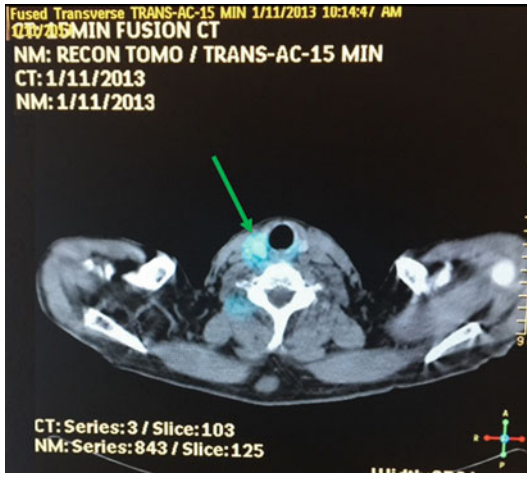

Fig. 40.7 Sample of an early (15 min post-injection) fused imaged demonstrating focal activity (*arrow*) in the right thyroid lobe and minimal activity in the left lobe

2. OSEM iterations: 2, maximum number of OSEM subsets:
   - 10, pre-filter Hann 0.9.
   - Post-filter Hann frequency 0.9, order 10.

Optional Maneuver

Initial early-only (15-min) images may be requested occasionally if the patient has already had a prior dual-phase parathyroid scintigraphy study performed. The radiotracer injected for this study is utilized for intraoperative localization purposes with a gamma probe.

General Image Interpretation

Initial images are evaluated by the interpreting physician for any intense focal uptake in the region of the thyroid gland (see Fig. 40.7), adjacent to the thyroid gland, or even in an ectopic location. This focus should persist on delayed images; the presence of greater washout of radiotracer from the thyroid gland as compared to the intense focus suggests the presence of a parathyroid adenoma(s). Occasionally, one may see a "rapid washout" parathyroid adenoma. SPECT-CT images are utilized as confirmation of an intense focus and for exact anatomic localization.

Picture Archiving and Communication System (PACS) Data (i.e., Recommendations on What to Send to PACS)

1. All PLANAR images at 15 min and 2 h in grayscale (Fig. 40.8).
2. CINE of SPECT at 15 min and 2 h in grayscale.
3. Multi-frame screen captures of SPECT at each time point (one each in axial, sagittal, and coronal planes) in grayscale.
4. Series of fused SPECT/CT axial images in "cool" from 15 min and 2 h.

Principal Radiation Emission Data and Dosimetry [9]

^{99m}Tc, physical half-life = 6.02 h.

Radiation Mean % Per Disintegration Mean Energy (keV)

Gamma 89 keV and 141 keV.
Gamma 91 keV and 2 keV.

Radiation Dosimetry for ^{99m}Tc-Sestamibi in Adults [2, 11]

Radiopharmaceutical	Administered activity (MBq) mCi	Organ receiving the largest radiation dose mGy/MBQ (rad/mCi)	Effective dose[a] mSv/MBQ (rem/mCi)
^{99m}Tc-sestamibi	185–923 IV (5–25)	0.038 Gallbladder (0.14)	0.0085 (0.031)

[a]International Commission on Radiological Protection. Radiation Dose to Patients from Radiopharmaceuticals. London: ICRP Publication: ICRP; 1988: 199,264.373. International Commission on Radiopogic Protection.

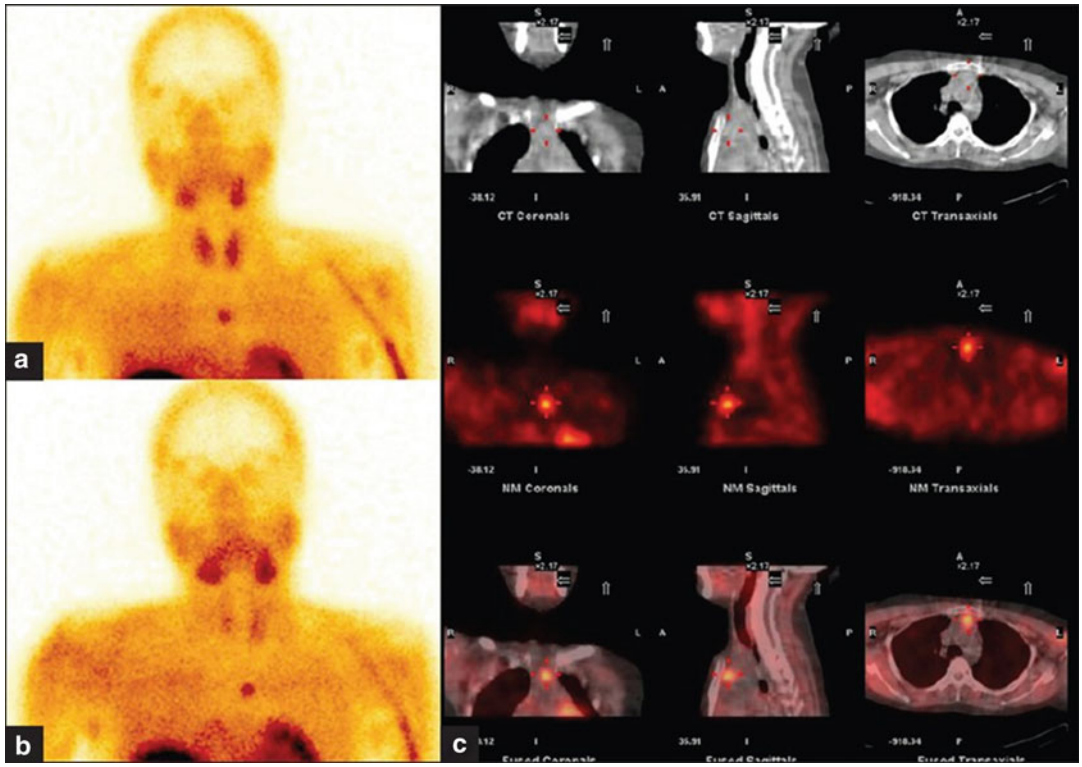

Fig. 40.8 Planar images (**a**, **b**) and CT, SPECT, and fused SPECT/CT images demonstrating an ectopic parathyroid adenoma in the anterior mediastinum [17]

Radiation protection in Biomedical Research. IRCP Publication 62, New York: Pergamon; 1993:23

Quality Control

In addition to the usual quality control measures for radiotracers and a gamma camera, it is very important to check for patient motion when SPECT-CT is performed as mis-registration can cause false localization of the parathyroid adenoma(s).

The patient should be imaged from the skull base to at least the mid-heart level in the mediastinum to prevent missing an ectopic adenoma [11].

Summary

^{99m}Tc-sestamibi is regarded as the radiopharmaceutical of choice, but some others have been used as follows [12]:

1. ^{99m}Tc-pertechnetate: This radiopharmaceutical is trapped in functioning thyroid tissue, and these images are subtracted from the ^{99m}Tc-sestamibi images. What remains after subtraction is activity in a potential parathyroid adenoma. The dose given is 74–370 MBq (2–10 mCi). Either radiopharmaceutical can be administered first, but if ^{99m}Tc-pertechnetate is given first, there is a waiting period of about 30 min before the 10-min images are obtained. Then there is another 10-min period after the administration of ^{99m}Tc-sestamibi before the 10-min images are acquired. However, if ^{99m}Tc-sestamibi is given first, 10-min images are obtained, and then the patient needs to be immobilized for 15–30 min after the ^{99m}Tc-pertechnetate injection before the 10-min images can be acquired [13].
2. 123-I [11]: This radiotracer has a half-life of 13 h, emits a photon of 159 keV, and is used to delineate the thyroid gland. This is done by

uptake of the 123-I into the follicular cells where it is trapped and then organified within the thyroid tissue. These images are then subtracted from the ^{99m}Tc-sestamibi images, and the remaining activity on the subtraction images suggests the presence of a parathyroid adenoma. The radiopharmaceutical is given orally in doses of 7.5–22 MBq (200–600 microCi). When this isotope technique is used, 123-I must always be administered first due to the lower activity and the longer time to accumulate in the thyroid gland. Images are therefore obtained 4 h after administration. ^{99m}Tc-sestamibi is then injected, and high-count images are taken after 10 min. Disadvantages of this technique include the high cost of 123-I and a longer time for the study to be completed [14]. Additionally, a history of iodinated contrast administration within the prior 4–6 weeks will compromise this study as the receptor sites for iodine on the thyroid cells may still be saturated resulting in inadequate thyroid images for subtraction [15].

QUICK REFERENCE GUIDE FOR PARATHYROID SPECT-CT:

PATIENT PREPARATION: None

RADIOTRACER: 99m-Tc-sestamibi, IV

ADMINISTERED ACTIVITY: 20 mCi

IMAGING PARAMETERS:
PATIENT POSITION: Supine
COLLIMATOR: High-resolution parallel-hole
FIELD-OF-VIEW: Base of brain to mid-heart
ENERGY WINDOW: 20% centered at 140 keV
MATRIX: 128 x 128
ZOOM: Zero

ACQUISITION:
1. **EARLY (**15 minutes after radiotracer injection):

PLANAR images in ANT, RAO, and LAO projections for 5 minutes/image

SPECT/CT: **SPECT**—Step-and shoot, 180 ° per detector, 60 steps, 40 seconds/stop; CT—140 kVp, 20 mAs

2. **DELAYED** (2 hours after tracer injection):

PLANAR IMAGES in ANT, RAO, and LAO projections for 5 minutes/image

SPECT-CT: SPECT—Step-and shoot, 180 ° per detector, 60 steps, 40 seconds/stop; CT—140 kVp, 20 mAs

SEND TO PACS:
1. All PLANAR images at 15-min and 2-hrs in grayscale.
2. CINE of SPECT at 15-min and 2-hrs in grayscale.
3. 3 Multi-frame Screen Captures of SPECT (1 each in axial, sagittal, and coronal plane) at 15-min and 2-hrs in grayscale.
4. Series of fused SPECT-CT axial images in "cool" (GE color scale) from 15-min and 2-hrs.

Society Guidelines

Society of Nuclear Medicine and Molecular Imaging [16]:

Greenspan BS et al. SNM Practice Guideline for Parathyroid Scintigraphy 4.0. J Nuc Med Technol. 2012; 40:**1-8.**

European Association of Nuclear Medicine Parathyroid guidelines [11]:

Hindie' E, Ugur O, Fuster D et al. 2009 European Association of Nuclear Medicine Parathyroid guidelines. Eur J Nucle Med Mol Imaging.2009 Jul:**36(7); 1201-16.**

Best Practices: N/A

Expert Opinion

Based upon current evidence, societal guidelines and peer-reviewed literary publications, the first-line modality for imaging of parathyroid adenomas is ultrasound and ^{99m}Tc-sestamibi imaging incorporating planar and SPECT/CT acquisitions for accurate localization within the neck as well as at suspected ectopic sites.

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Radiation Dose to the Patient from Parathyroid Imaging

41

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Contents

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Radiation Overview

Types of Radiation

There are many ways to describe radiation dose to the patient. Clustering the types of radiation into their ability to impart an effect on the human body can be a utilitarian approach. Ionizing radiation versus non-ionizing radiation is a generalization which describes the degree of an effect a type of radiation will have on the human body.

Non-ionizing radiation has enough energy to cause atoms in a molecule to move around or vibrate. Ionizing radiation has a higher range of energy that can remove electrons from atoms and disrupt the body on a cellular level. Thus ionizing radiation causes a greater degree of interaction with the body—some of which can be harmful. Examples of ionizing radiation include the cosmic rays while traveling in aircraft, the common X-ray, and computer-assisted tomography (CT) imaging.

The Effects of Ionizing Radiation

Stochastic and deterministic are two types of effects which ionizing radiation can have. Stochastic effects deal with probabilities. A stochastic effect is the probability that a genetic

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effect of a cancer will be induced. An example of a stochastic effect could be a radiation worker from the Chernobyl accident, spring 1986. Years later, a person may or may not develop a malignancy directly attributable to that exposure.

Deterministic effects are quantifiable responses to an exposure to an ionizing radiation. Examples of deterministic effects from ionizing radiation include skin erythema, hair loss, and certain blood abnormalities.

Quantifying Radiation Exposure

Radiation dose is the mean energy imparted, per unit mass, by ionizing radiation. It is measured in a unit called gray (Gy) [non-SI: rad (rad)]. One Gy is defined as a Joule/kilogram [non-SI: one rad is defined as 100 erg/gram]. While a Gy is a physical quantity, a Sievert (Sv) is an SI unit of measure describing the health effects of ionizing radiation. The two are related by a dimensionless factor W (radiation weighting factor) which varies depending upon the incident radiation. For our consideration, Gray and Sievert are equal. Further, various types of radiation have different effects—which is the source of W. An example of this would be having a ping pong ball thrown against a wall at 100 MPH as compared to having a bowling ball thrown at a wall at 100 MPH. Clearly, the bowling ball would do more harm to the wall—just like different types of radiation do different amounts of harm and thus have different radiation weighting factors.

Within the body, different organs and cell lines have different sensitivities to radiation. For example, exposing rapidly evolving gastrointestinal tissue and relatively stagnant nervous tissue to the same quantity and type of radiation would have a much more severe effect on the gastrointestinal tissue —as it is more sensitive. To account for the difference in sensitivities within the body, a measure of "dose equivalent" is used. Dose equivalent is measured in Sievert (Sv) [non-SI: roentgen equivalent man (rem)]. Some of the more radioresistant organs include the skin, bone surfaces, and the brain. Some of the more radiosensitive organs include the breasts, the gonads, red bone marrow, and the gastrointestinal tract.

Imaging Modalities Used to Assess the Parathyroid

Sources of Non-ionizing Radiation

The world is filled with sources of non-ionizing radiation all around us. Nonmedical examples of non-ionizing radiation include AM/FM radio, magnetic fields from overhead power lines, and microwave ovens. Sources of non-ionizing radiation used for parathyroid imaging include ultrasound and nuclear magnetic resonance imaging (MRI).

For the purposes of this chapter, we shall not consider ultrasound and MRI as significant contributors to the radiation burden a body undergoes during parathyroid imaging. It is conceded that ultrasound may be the most prevalent tool used to evaluate parathyroid glands and that MRI may be the preferred anatomic evaluation technique.

Sources of Ionizing Radiation

There are many sources of ionizing radiation in our world as well. Some examples include medical X-rays (for example when one breaks an arm), linear accelerators used to treat cancer patients, and irradiators used to sterilize medical products and equipment as well as foods and spices. Sources of ionizing radiation used for parathyroid imaging include CT imaging and nuclear medicine studies.

CT Imaging Basics

During certain conditions, an abnormality of the parathyroid glands may be identified during routine CT imaging. If the imaging was performed with an intravenously administered iodinated contrast agent (IV CON), it may be easier to identify the parathyroid glands. Recently there have been protocols developed describing assessment of the parathyroid, using IV CON, at multiple time points, as the contrast agents enter and wash out of the parathyroid glands. This approach can be referred to as 4DCT.

Nuclear Medicine Basics

Modern nuclear medicine uses 99m-Technetium (Tc-99m) as the radiopharmaceutical of choice to evaluate the parathyroid glands. It predominantly undergoes isomeric transition and emits gamma radiation with energy close to 140 keV. It has a half-life of approximately 6 h.

Commonly, Tc-99m is attached to a pharmaceutical which takes advantage of the physiology of the parathyroid gland. For parathyroid imaging, Tc-99m is often attached to a compound called sestamibi: methoxyisobutylisonitrile. For simplicity, Tc-99m attached to sestamibi shall henceforth simply be called "mibi." Mibi undergoes oxidative phosphorylation within mitochondria. The parathyroid glands can be rich in mitochondria, making mibi an ideal imaging aid. The most common modern application of mibi is an early planar image, routinely 15 min after mibi injection and a second planar image 2 h after mibi injection. Planar images are normally acquired from the angle of the mandible through the aortic arch. Many institutions also perform single-photon emission computer-assisted tomography (SPECT), often with a coincidentally acquired CT (SPECT/CT). Theoretically, there is an advantage to doing SPECT/CT at the earlier time point, assuming that there may be presence of a rapid washout adenoma. The normal dose used is 740-1,110 MBq (non-SI: 20-30 mCi). When CT is used, it has been suggested to use a tube current between 100 and 200 mAs, with a voltage of 100–140 kVp [1–3]. The advantage of including SPECT/CT, as opposed to only planar mibi imaging, is to provide better anatomic localization for the head and neck specialty surgeon.

Classically, imaging was performed with Tc-99m-pertechnetate; which is to say that the Tc-99m was not attached to any "uniquely" metabolic structures. In effect, it was akin to balancing an ionic charge with a salt. Moreover, some institutions have used thallium-201, 99m-Tc-tetrofosmin, and 123-I for parathyroid imaging. In theory, 18-F-fluorodeoxyglucose (FDG) or 11-C-methionine (C11) positron emission tomography (PET) CT (PET/CT) could be used for imaging as well. Mibi imaging is the focus of this chapter.

Uses of Imaging in Parathyroid Gland Evaluation

The predominant role of imaging the parathyroid gland is to evaluate the gland's anatomic location. Knowing an exact anatomic location allows the surgeon to perform a less invasive surgery. Frequently, imaging is also used to assess for ectopia. Parathyroid glands can be located anywhere between the tongue and the mediastinum. If one were to simply evaluate the neck with an ultrasound or only perform a head and neck CT, ectopic parathyroid glands could be missed. Nuclear medicine mibi scans are particularly adept at assessing for ectopia. However, 4DCT or MRI can accomplish this role as well.

Dose to the Patient

Dose from 4DCT

Using an anthropomorphic phantom and 4DCT (64-MDCT, 750 HD, GE Healthcare) acquired over three phases, 0.625 mm thickness, 0.4-s tube rotation time, 0.516:1 pitch, 20 cm FOV, 120 kVp, and 100–700 mAs based upon automatic modulation), Hoang reports highest radiation doses to the thyroid (150.6 mGy) and salivary glands (137.8 mGy). This corresponds to an effective dose of 28 mSv [4].

While phantom modeling may be reproducible, there is great variability from institution to institution, not only in the technique of acquiring 4DCT, but also in the actual CT scanning hardware itself. Some institutions acquire only two CT scans, while others acquire four CT scans, both with a mixture of non-contrast-enhanced and contrast-enhanced time points. Another study modeling a 4DCT approach (64-MDCT, 750 HD, GE Healthcare, acquired over four phases, 0.8-s tube rotation time, 0.984:1 pitch, 120 kVp, and 160 mAs {it is unclear how this would compare to automatic tube current modulation imaging}) and

estimating effective dose with the Imaging Performance Assessment of CT Scanners (ImPACT) calculator, version 1.0.3, calculated that their technique would yield an effective dose of 10.4 mSv [5]. A recent study assessing 119 patients undergoing 4DCT at one institution reported mean effective dose of 5.56 mSv. However, the only acquisition data reported were that 1.25 mm slices were used [6].

Dose from Mibi

Using estimates from the International Commission for Radiological Protection (ICRP) report 80, with a presumed administered activity of 25 mCi of mibi and an attenuation correction CT acquired at 3.75 mm thickness, 0.8-s tube rotation time, 1.375:1 pitch, 50 cm FOV, 120 kVp, and 80 mA, Hoang reports highest radiation doses to the colon (41.5 mGy), gallbladder (39.8 mGy), and kidneys (32.3 mGy). This corresponds to an effective dose of 12 mSv [4]. Another modeling study used the Medical Internal Radiation Dose (MIRD) technique, and reported an effective dose of 7.8 mSv, when 20 mCi of mibi was administered and no CT was performed for SPECT attenuation correction [5].

When 10.2–20.5 mCi of mibi was administered to 144 patients, in a study by Madorin, it was estimated that the mean effective dose was 3.33 mSv; yet it is unclear if attenuation correcting CT was used—presumably, it was not [6].

Impact of 4DCT and Mibi Doses (Table 41.1)

Considering Hoang's data and using modeling from the Biologic Effects of Ionizing Radiation (BEIR) VII report, a 55-year-old woman undergoing 4DCT would incur an increased incidence of cancer, over baseline, of 0.52 %. Using a similar assessment, for a mibi scan, she would incur an increased incidence of cancer, over baseline, of 0.19 % [4].

As background, the average US background radiation exposure is 3 mSv/y. A US radiation worker is allowed to receive a maximum of 50 mSv/y. A representative chest CT often comes at a cost of approximately 7 mSv. When delivered in an acute manner, 400 mSv may induce initial signs of acute radiation sickness.

Table 41.1 Comparison of effective doses from various radiologic studies

Effective doses on gender-averaged and age-averaged adults 18–64, from ICRP-103.		
	Average effective dose (mSv)	Lifetime risk of a cancer-caused death
Parathyroid scan (mibi)	6.4	1 in 3600
CT (neck)	3	1 in 8000
Effective doses from 4DCT, as reported by different authors		
4DCT [4]	28	
4DCT [5]	10.4	
4DCT [6]	5.56	
Other radiologic examinations using ionizing radiation, provided for comparison		
Chest X-ray (PA + lateral)	0.05	1 in 480000
CT (chest)	7	1 in 3500

Summary

While there are a variety of CT acquisition techniques to achieve 4DCT, across the board the effective dose is greater than with mibi. However, the clinician and patient together must take into consideration the risk-benefit ratio of 4DCT versus mibi. 4DCT may confer a larger effective dose, and for elderly patients, this increased effective dose may be justified. Given the relationship of thyroid cancer and age, some suggest caution when considering 4DCT for female patients aged 30 and younger and for male patients aged 20 and younger [5, 7]. Some suggest reserving 4DCT for cases of failed parathyroidectomy or in cases of altered anatomy [8].

Lastly, consideration for the surgical team should be remembered. Some institutions mitigate the surgical team's exposure by administering mibi one day and performing surgery the following day, often using an intraoperative gamma probe. However, when 4DCT is used, there is no time constraint for the surgical team.

Society Guidelines

1. Hindie E, Ugur O, Fuster D, et al. 2009 EANM parathyroid guidelines. Eur J Nucl Med Mol Imaging 2009; 36:1201–16.
2. ACR-SNM-SPR practice guideline for the performance of parathyroid scintigraphy.2009.
3. Greenspan BS, Dillehay G, Intenzo C, et al. SNM practice guideline for parathyroid scintigraphy 4.0. J Nucl Med Tech 2012; 40(2).

Best Practices: N/A

Expert Opinion

Parathyroid imaging has evolved significantly, and it continues to evolve. Planar imaging may offer increased comfortability to the patient and less radiation, but the addition of a correlative CT offers an advantage to the head and neck surgeon.

Using current CT techniques, the radiation doses are somewhat comparable between 4DCT and nuclear medicine techniques. However, with time, assuredly the dose from 4DCT will come down and confer a clear advantage.

At our institution, both practices are used, and both provide appropriate results to the surgeons, the interpreting NM physician, and the patient. Perhaps a clear advantage will declare itself in the future. Perhaps that advantage will be contrast-enhanced MRI.

Disclaimer The views expressed herein are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

References

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42 Laboratory Testing, PTH Measurement of Needle Aspirates, and Intra Operative PTH Technologies

Joshua A. Bornhorst, Aime T. Franco, and Andrew M. Hinson

Contents

Introduction

Parathyroid hormone (PTH) is synthesized by the parathyroid glands and secreted directly into circulation in order to regulate calcium and phosphate homeostasis. The full-length hormone, which is comprised of 84 amino acids, has a plasma half-life of less than 5 min. PTH is measured to aid in the differential diagnoses of calcium-related disorders and to monitor bone metabolism in patients with chronic kidney disease. Rapid PTH assays are currently the best intraoperative adjunct for monitoring for an adequate response to resection of one or more hyperfunctional parathyroid tumor(s). Significant variability exists among commercially available PTH assays. This chapter describes these assays and their relative characteristics.

Pre-analytical Variability

Circulating Heterogeneity

$PTH_{1–84}$ is synthesized and secreted by the parathyroid glands largely in response to changes in serum calcium [1, 2]. Circulating PTH fragments, containing carboxyl (C)-terminal or amino (N)-terminal peptides, arise from the intraglandular (chief cell) and peripheral (primarily hepatic) degradation of $PTH_{1–84}$ [3, 4]. While the

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half-life of $PTH_{1–84}$ is between 2 and 4 min, the half-life of C-terminal fragments ranges between 10 and 50 min [5, 6].

In the setting of normocalcemia, the composition of PTH in circulation is approximately [6–8]:

$PTH_{1–84}$	20 %	(Range 5–30 %)
N-terminal fragments	2 %	(Range 0–5 %)
C-terminal fragments	80 %	(Range 75–95 %)

PTH with an N-terminal structure (or the first 34 amino acids) is biologically active and equipotent compared to the full-length hormone. For example, recombinant $PTH_{1–34}$ or teriparatide (Forteo®, Eli Lilly and Company) is a widely available drug for men and women with severe osteoporosis [9]. Despite the biological significance of $PTH_{1–84}$ and $PTH_{1–34}$, these molecular forms account for only a fifth of total PTH in circulation.

C-terminal fragments, in contrast, account for most (~80 %) of the PTH in circulation. While historically regarded as biologically inert, increasing evidence suggests that some C-terminal fragments can interact with non-classical PTH receptors and induce biological actions that are independent and opposite to those of $PTH_{1–84}$ or $PTH_{1–34}$ [6, 10]. Small C-terminal fragments, which altogether lack a N-terminal structure (e.g., $PTH_{37–84}$, $PTH_{38–84}$), are the most prevalent molecular form in circulation (~70–75 %). Large C-terminal fragments (e.g., $PTH_{7–84}$), which are often referred to as non-$PTH_{1–84}$ in the literature and have truncated N-terminal structures, are relatively less common but can accumulate in the setting of renal failure [7, 11–13].

Pathophysiological Variability and Expected Results

There is inherent biological variability in PTH patterns over time; in general, PTH levels rise with age and body mass index [14]. In healthy persons, PTH secretion is circadian, with the highest levels being released in the nighttime hours [15–18]. Physical exercise and seasonal behaviors can also influence PTH levels [19].

PTH levels also vary according to changes in serum calcium and renal function. In the setting of hypercalcemia or elevated $1,25(OH)_2D$, PTH secretion is reduced but favors a relatively higher C-terminal fragment to $PTH_{1–84}$ ratio [3, 6, 20]. Concurrent high calcium and high PTH concentrations may indicate an etiology of primary hyperparathyroidism while the absence of PTH elevation may indicate hypercalcemia of malignancy.

In the setting of acute or chronic hypocalcemia, the parathyroid glands secrete primarily $PTH_{1–84}$ and few C-terminal fragments. Concurrent low PTH and calcium levels are indicative of hypoparathyroidism (e.g., postsurgical or idiopathic etiology). Elevated PTH concentration in the absence of hypercalcemia is consistent with secondary hyperparathyroidism, which is often caused by hypovitaminosis D or reduced renal function. Continual overproduction of PTH results in renal osteodystrophy [21–23].

Analytical Determination

Competitive (First-Generation) Assays

In 1963, Berson and Yalow developed the first radioimmunoassay for PTH [24] (Fig. 42.1). Their early first-generation (competitive) assay employed polyclonal sera from guinea pigs and rabbits raised against bovine PTH [24]. Because of the assay's low sensitivity, circulating PTH levels had to be significantly elevated (e.g., patients with hyperparathyroidism) to be detected. A decade later, Arnaud and colleagues (Mayo Clinic) enhanced the assay's sensitivity for human PTH by using antibodies raised against porcine (rather than bovine) PTH, which allowed for measurement of PTH levels within the normal human range [25].

Fig. 42.1 The first PTH assay. Solomon Berson and Rosalyn Yalow first measured PTH via a radioimmunoassay in the early 1960s. In 1977, Dr. Yalow won the Nobel Prize for radioimmunoassay measurement of peptide hormones (including PTH); Dr. Berson died from a heart attack in 1972

Intact (Second-Generation) Assays

However, because of high cross-reactivity with small C-terminal fragments and insufficient sensitivity for measuring intact hormone, first-generation assays were replaced by two-site (noncompetitive) immunometric or "sandwich assays" [26]. Second-generation or "intact" PTH assays employ a C-terminal capture antibody (e.g., epitopes 39–44) bound to a solid phase and a second enzyme-labeled N-terminal reporter or signal antibody (e.g., epitopes 13–34) [27] (Fig. 42.2).

While initially thought to measure only intact hormone, later characterization of the assay demonstrated that the detection antibodies cross-react with large C-terminal fragments, which have truncated N-terminal structures (e.g., $PTH_{7–84}$) [12]. Depending on the assay, large C-terminal fragments can account for up to 10–30 % of immunoreactive PTH in patients with normal renal function, and up to half in patients with renal failure [6, 13]. Despite these limitations, intact assays are still widely used in many clinical laboratories, and reliable reference ranges have now been established in many patient populations.

Bioactive (Third-Generation) Assays

To eliminate cross-reactivity with all C-terminal fragments, third-generation or "bioactive" ("whole" or "bio-intact") PTH assays were developed. Bioactive PTH assays employ a similar capture antibody compared to intact assays but use detection antibodies directed against epitopes located at the extreme N-terminal region (e.g., epitopes 1–4) [28–31] (Fig. 42.2).

The detection antibodies were later demonstrated to cross-react with yet another PTH molecular form, which had not previously been appreciated [32]. This newly discovered molecular form, referred to as N-PTH, is not a PTH fragment but rather a posttranslational modification (possibly a phosphorylated serine at position 17) of $PTH_{1–84}$ [28, 30, 31, 33]. Because the modification exists within epitopes 15–20, intact assays do not detect N-PTH. While the physiological relevance of the modified PTH remains unknown, N-PTH appears to be over-secreted in the setting of severe hyperparathyroidism and in parathyroid cancer [34, 35].

Because bioactive assays do not cross-react with large C-PTH fragments, the third-generation-to-second-generation PTH ratio is

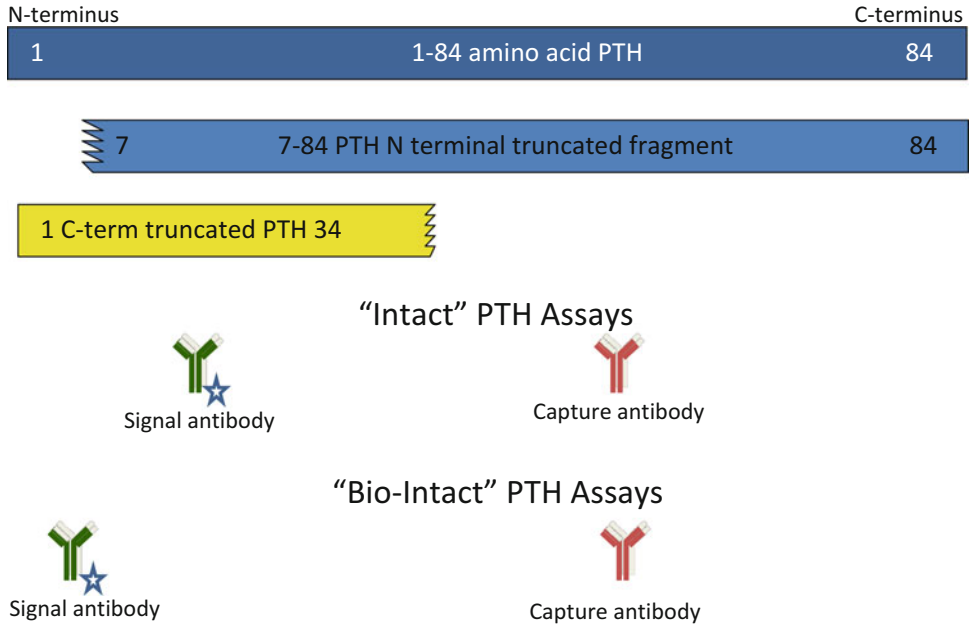

Fig. 42.2 Immunometric PTH assays. Intact PTH assays employ a C-terminal (e.g., epitopes 39–44) capture antibody bound to a solid phase and a second enzyme-labeled N-terminal (e.g., epitopes 13–34) reporter or signal antibody. Third-generation or bioactive ("whole" or "bio-intact") assays employ a similar capture antibody compared to intact assays but use detection antibodies directed against epitopes located at the extreme N-terminal region

generally less than one. However, in the setting of parathyroid cancer, this does not appear to be the case. Interestingly, a third-generation-to-second-generation PTH ratio >1 has a sensitivity of 83.3 %, and a specificity of 100 % for diagnosing parathyroid carcinoma in patients presenting with primary hyperparathyroidism [34, 35]. While more studies are needed, this ratio may be a useful adjunct for diagnosing parathyroid carcinoma earlier in the disease course, and identifying those patients who are at higher risk for recurrent disease [34, 35].

Next-Generation Assays

Liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) detection has traditionally been limited to the quantitative analysis of small molecules (e.g., testosterone, vitamin D metabolites). However, MS techniques are rapidly being developed and refined for their ability to quantify larger and more complex molecules, such as $PTH_{1–84}$ [36]. To date, the primary challenge preventing widespread implementation of MS for PTH measurement is the significant amount of interference caused by several different modified PTH molecular forms (e.g., oxidized and phosphorylated PTH variants), which can rapidly accumulate in some patient samples. For example, in patients requiring dialysis, a large proportion of PTH becomes oxidized and biologically less active. Thus, results obtained using conventional assays (which include non-oxidized and oxidized PTH) likely over-estimate the true level of biologically active hormone in this patient population.

With this in mind, a variant of the intact PTH assay was recently developed to help improve the specificity of PTH measurements in dialysis patients. First, a monoclonal antibody is used to immobilize and subsequently eliminate all oxidized PTH (identified via methionine residues located at position 8 and/or 18); all remaining PTH is then measured with a conventional intact assay, which employs antibodies against epitopes

26–32 and epitopes 55–64 for capture and detection, respectively [37]. In the original study, a large (but highly variable) proportion (~90 %) of the starting PTH concentration in the dialysis patient samples were determined to be oxidized (biologically less active) [37]. While promising, the clinical implications of differentiating oxidized versus non-oxidized PTH in circulation remain speculative.

Collection, Storage, and Potential Contaminants

Approximately 3–4 mL (minimum 1 mL) of whole blood is collected via venipuncture in a pre-chilled EDTA plasma tube (lavender top). After collection, EDTA whole blood is centrifuged immediately. To avoid hemolysis (which decreases PTH values), the collection tube should not be filled completely, and the sample should remain relatively stable and upright throughout collection, transport, and processing. The specimen is then gently inverted (but NOT shaken) several times to allow mixing. EDTA whole blood is stable for a maximum of 2 h at ambient temperature and 4 h on wet ice.

> [*Note: Serum (red top) tubes, while a less stable reservoir for PTH compared to EDTA plasma, are also acceptable. However, when using serum tubes, the whole blood sample must be allowed to clot, which can take approximately 30 min (potentially longer in patients receiving anticoagulation therapy) after sample collection. Centrifuging serum samples before clotting occurs can result in fibrin formation. While the time required for whole blood to clot may not be critical for routine clinical or laboratory testing, it can be a source of significant delay in the intraoperative setting (see below).*

The plasma (anticoagulated blood) or serum (after a clot has formed) is then separated from the supernatant using a refrigerated centrifuge (10 min at $2095 \times g$). After centrifugation, EDTA plasma is stable for approximately 4 h at ambient temperature, 24 h at 4 °C, 2–4 months at −20 °C, and 2–24 months at −80 °C [38]. Of note, bioactive (third-generation) assays are associated with greater PTH stability compared to their intact (second-generation) counterparts [39].

Heterophile antibodies in human serum, which may be present in up to 11 % of the population, can potentially bridge the assay immunoglobulins (i.e., the capture and signal antibodies) and falsely elevate in vitro diagnostic results [19, 39, 40]. Heterophile antibodies are becoming increasingly prevalent in the USA because of enhanced exposure to monoclonal antibodies for the treatment of chronic inflammatory disorders, cancer, and transplantation [40]. When heterophile antibodies are suspected, re-analysis of the patient's serum may be performed using blocking agents that are specific to the immunoassay [40]. Unusual fragments or genetic variations in PTH have been implicated in falsely low measured PTH concentrations for some assays [41].

PTH Standards and Reference Intervals

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) established a PTH working group with the intentions of (1) "[defining the] inclusion/exclusion requirements for an appropriate panel of sera and plasma with which to establish reference intervals and establishment of such a panel with support from the clinical community and diagnostic manufacturers," and (2) "development of a reference measurement procedure for $PTH_{1–84}$ to a standard that would enable its adoption by the IFCC reference laboratory network [42]."

Thus, at present, there remains no PTH standard or reference by which to compare PTH assays, and there is little to suggest that any such announcement is coming any time soon. Regardless of whether a PTH standard is available or not, best practice in regard to measuring PTH in human circulation always involves knowing what the assay *actually* measures and interpreting assay results in the context of other laboratory parameters, in addition to the patient's clinical history and exam findings.

Modern or commercially available PTH assays (i.e., intact and bioactive assays) generally yield reference intervals somewhere between 10 and 100 pg/mL. Intact and bioactive assays pos-

sess sufficient sensitivity and reproducibility to measure PTH concentrations at the low end of the reference range in the normal population (~10 pg/mL) [43]. When reference subjects with vitamin D levels less than 20 nmol/L (which raises serum PTH levels) are excluded, the upper limit of the normal population PTH reference interval is approximately 50 pg/mL.

Significant variability in results obtained by immunometric assays has repeatedly been demonstrated in the literature [44]. Despite all of the discrepancy, there are no known clinically significant differences in the diagnostic sensitivities between intact (second-generation) and bioactive (third-generation) assays for the diagnosis of primary hyperparathyroidism in patients with normal renal function [45–48]. Moreover, bioactive PTH assays have not yet proved any significant advantage over intact assays in the diagnoses of bone disease or other clinical manifestations of secondary hyperparathyroidism in uremic patients [45].

Assays belonging to the same generation can vary by as much as 4.2-fold in magnitude between the lowest and highest reading methods [44, 49, 50]. The difference in the PTH levels between any two assays, however, is generally proportional throughout the range of measurements. There is some evidence that applying dynamic reference intervals (based on a range of serum PTH values obtained by acute modification of serum calcium concentrations in healthy subjects) instead of Gaussian intervals (based on PTH values observed in individuals with normocalcemic concentrations) may significantly improve the clinical sensitivity of PTH assays ([51]; Lepage 1988). In one study, dynamic reference intervals increased the average clinical sensitivity for detecting primary hyper- and hypoparathyroidism from 68 to 100 % [51].

Intraoperative PTH Assays

Rapid PTH Model

In 1988, Samuel Nussbaum (Massachusetts General Hospital) and colleagues presented a small case series ($N = 13$) at the American Association of Endocrine Surgeons (AACE) meeting in Boston suggesting that their PTH immunoradiometric assay (turnaround time 15 min) could be used as an intraoperative adjunct for guiding the extent of neck exploration during parathyroidectomy [27]. In 1993, after Nichols Institute Diagnostics had made available the equipment and labeled antibody for use in an immunochemiluminometric (no longer requiring radioactive isotopes) assay, Dr. George Irvin (University of Miami, Jackson Memorial Hospital) popularized the assay as an adjunct to image-guided, focused parathyroidectomy [52].

Because the plasma half-life of PTH is less than 5 min, intraoperative PTH monitoring enables the surgeon to detect a decline in PTH after the primary source(s) of the excess hormone is excised. The Miami criterion, established by Irvin and continuing to be used today, requires obtaining at least four intraoperative PTH samples (pre-skin incision, pre-gland excision, 5 min post-gland excision, 10 min post-gland excision). A 50 % reduction in PTH levels at 5 or 10 min post-excision is indicative of surgical success. The criteria can be modified or adapted depending on the desired sensitivity and/or specificity [5, 53–55]. For example, many surgeons often also obtain a 20-min sample after gland removal if there is a delayed drop in PTH, which does not meet or is close to the 50 % requirement, before continuing further exploration.

Rapid PTH assays have a turnaround time ranging between 8 and 20 min. Some manufacturers offer a relatively "slower" laboratory mode for routine clinical analysis and a "faster" (e.g., "rapid" or "turbo") mode for intraoperative analysis. For example, the Access® Immunoassay System (Beckman Coulter, Pasadena, CA) offers "routine" (~30 min) and "intraoperative" (~15 min) modes. According to the manufacturer, when PTH levels are >12 pg/ml, the routine and intraoperative modes' imprecision levels are ≤8 % and ≤12 %, respectively. In our experience, the Beckman intraoperative mode yields about 5 % lower PTH levels compared to the routine mode and the differences in precision were within the manufacturer's reported ranges (7 % vs. 6 %).

Table 42.1 Commonly used commercially available (past and/or present) intraoperative PTH assays

Platform (manufacturer)	Setting	Form	Fragments	Reference (pg/ml)	Time (min)
STAT-IO-I-PTH (Future Diagnostics)	Point of care	Intact	$PTH_{1–84}$ Non-$PTH_{1–84}$	10–65	8
Advantage[a] (Nichols Diagnostics)	Point of care	Bioactive	$PTH_{1–84}$ N-PTH	6–40	12
Access Intraoperative Mode (Beckman Coulter)	Central Lab	Intact	$PTH_{1–84}$ Non-$PTH_{1–84}$	12–88	15
Turbo Intact PTH (Diagnostic Products)	Central Lab	Intact	$PTH_{1–84}$ Non-$PTH_{1–84}$	12–72	16
Elecsys 2010/1010/E170 Stat Assay (Roche Diagnostics)	Central Lab	Intact	$PTH_{1–84}$ Non-$PTH_{1–84}$	15–65	9

[a]The Nichols Advantage kit was introduced in 1996 and was the first widely available rapid intraoperative PTH assay. The US Food and Drug Administration removed the assay from the market in 2005 [57]. Future Diagnostics (Wijchen, Netherlands) released a new version of the point-of-care (POC) intraoperative PTH assay called the STAT-IO-I-PTH

See Table 42.1 for other commonly used and commercially available (past and present) intraoperative PTH platforms.

While statistically significant variations among various intraoperative assays have been reported (predominantly in the setting of renal insufficiency), the clinical significance of the variation among commercially available assays is not well established. Technical and patient factors that can cause an insufficient decline in PTH levels include decreased renal clearance in patients with chronic renal disease, significant baseline sample hemolysis or hemodilution (both decrease baseline PTH value), a missed peak, and laboratory errors. Technical factors such as post-excision sample dilution or hemolysis (both decrease PTH value) can lead to a falsely adequate drop in PTH, which in turn can lead to missed parathyroid disease.

Cost-Effectiveness of Intraoperative PTH Monitoring

The cost-effectiveness of intraoperative PTH monitoring is difficult to measure because one must balance the ability of the technique to prevent missed multiglandular disease with the total assay-related costs over time [56]. Additionally, a number of institution-specific factors influence the relative value of intraoperative PTH monitoring. Total assay costs include the platform/instrumentation, reagents, quality controls, calibration material, labor, inspection/service, repairs, and operating room time.

In a literature review involving 4280 patients identified in 17 different studies, Morris et al. concluded that intraoperative PTH monitoring increases the cure rate of minimally invasive parathyroidectomy only marginally (98.8 % vs. 96.3 %) while incurring approximately 4 % additional cost. However, intraoperative PTH monitoring can potentially compensate for itself by reducing operating room times and eliminating the need for frozen sections. Intraoperative PTH reduced overall treatment costs only when total assay-related costs were less than $110 per case (Fig. 42.3). The intraoperative PTH assay was cost saving when the rate of unrecognized multiglandular disease exceeded 6 % or if the cost of the reoperation exceeded $12,000 (compared with initial minimally invasive parathyroidectomy, $3733).

An emerging debate among those who use intraoperative PTH monitoring routinely is whether it costs more or less to perform the PTH assay at the point of care (POC) or via a central laboratory. If POC testing decreases operating room time (estimated at $88–$94 per min), then high-volume thyroid and parathyroid surgical centers may experience considerable cost savings

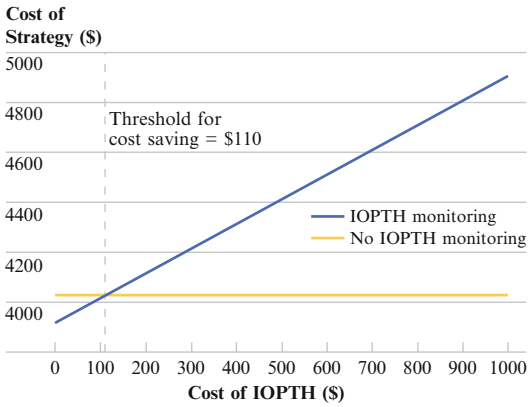

Fig. 42.3 Cost threshold for intraoperative monitoring. Intraoperative PTH monitoring is cost saving when the test-related costs fall below $110. This value considers both the cost of the test and the cost of the operating room time spent waiting for results. Permissions: Morris LF, Zanocco K, Ituarte PHG, et al. The value of intraoperative parathyroid hormone monitoring in localized primary hyperparathyroidism: a cost analysis. Ann Surg Oncol. 2010; 17:679–85

(e.g., $1400 per patient, assuming that POC testing reduces OR time by 17 min) [57, 58]. However, POC assay savings are offset, at least in part, by capital costs of equipment (~$30,000), higher reagents/quality control costs (central lab $3.61 vs. POC $37), and labor (~$28 per hour) [59].

Needle Aspirates

Intraoperative PTH, which is obtained by fine-needle aspiration (FNA), can be used to differentiate parathyroid from non-parathyroid tissue (e.g., thyroid, lymph node, thymus, muscle, fat) with a specificity of 100 % [60, 61]. Generally, FNA is performed with a 3- or 5-mL syringe and a 23- or 25-G needle. The desired tissue is drawn into the syringe and then diluted in about 3 mL of normal saline. The sample is then agitated and centrifuged. The supernatant is analyzed using conventional intraoperative PTH measurements [62, 63]. While the risks of this procedure may be low, they are not negligible and can be severe (e.g., infection, hemorrhage) [64, 65].

Evidence on the efficacy of FNA PTH concentration determination methods as a surrogate "biochemical frozen section" has continued to accumulate [66]. In a large study of 255 parathyroid aspirates and 104 non-parathyroid aspirates, a median (with ± S.D.) of 8120 ± 2711 was found in parathyroid gland tissue aspirates versus 0.8 ± 9.29 for non-parathyroid aspirates. In this large study, the use of PTH measurements of FNA tissue aspirates was 100 % sensitive and 100 % specific, which has also been observed in other studies [62, 67]. Much less distinction in PTH concentrations and a lack of complete sensitivity and specificity have been seen in comparing pathological and non-pathological parathyroid glands [67]. Using POC PTH measurements resulted in a reduction in assay time of 12 min versus 19 min for frozen section results in one institution, although a large number of factors can influence relative times of the two investigations [62].

Alternatively, a "Na-wash" or saline washout method can be utilized in conjunction with cytology. In this method, following collection of cytology samples, FNA saline washes are obtained by washing the empty FNA syringes with 0.5–1.0 mL of saline. Washes from multiple needles can then be pooled and the subsequent saline solution analyzed by PTH determination. Utilizing the Na-wash technique, a comparison of parathyroid FNA determination with a PTH washout procedure exhibited a sensitivity of 84 % and specificity of 100 %, resulting in a positive predictive value of 100 % for parathyroid tissue. In this study, an arbitrary cutoff of 1,000 pg/mL was used for detection of parathyroid tissue. The authors indicated that this cutoff could be lowered. Importantly, this study seemingly indicated that in patients with difficulty in localization of a parathyroid adenoma, FNA with PTH determinations performed better than parathyroid scanning or ultrasonography alone [65]. In addition, the ability of the washout technique to reliably distinguish parathyroid tissue from other tissue has been shown to have application in thyroidectomy to prevent inadvertent damage to the parathyroid [68].

There are analytical considerations or potential interferences for the measurement of PTH in

saline solutions as described previously for plasma PTH. Again, PTH measurements vary widely between different PTH assays. As these sample types are much less well characterized, appropriate cutoffs are not well established and are often arbitrary and technique dependent. Published cutoffs for detection of parathyroid tissue, while not always rigorously evaluated, are relatively similar (100 and 138 pg/mL, for example) [64, 66]. Caution should be used in consideration of appropriate cutoff levels, as they will affect observed sensitivity and specificity. Ideally, some form of validation of the appropriateness of cutoff levels should be attempted in individual institutions. Furthermore, while the PTH assays used to determine PTH in plasma have been FDA approved, they are not approved for alternate sample types such as saline washes from tissue aspirates.

Thus, these assays used in conjunction with saline sample are considered laboratory-determined testing and require additional stability and accuracy validations, as there may be matrix affects or differences in stability as compared to plasma PTH determinations. Furthermore, if proposed FDA guidelines on laboratory-determined tests are finalized, extensive laboratory validation may be required, potentially limiting testing availability for non-validated specimen types [69].

Summary

Measuring PTH in circulation is an important element of the diagnostic assessment for hypocalcemia, hypercalcemia, metabolic bone disease, and parathyroid gland tumors. Assay techniques have evolved over the past 50 years in parallel with our understanding of the PTH molecule. Major advances include the use of nonradioactive isotopes, increased sensitivity and specificity for "intact" or "bioactive" hormone, and reduced incubation times. Intact or bioactive PTH hormone is highly labile and subject to fragmentation. Instability of the molecule is largely dependent upon time and temperature. The ability to rapidly and adequately test for intraoperative PTH has spurred a number of applications and surgical improvement.

Society Guidelines

- CKD-MBD: Monitor serum levels of calcium, phosphorus, PTH, and alkaline phosphatase activity beginning in CKD stage 3 (adults) and in stage 2 (children).

Best Practices

- Assay-specific normative ranges should be established for each assay before making therapeutic decisions for individual patients. This includes establishing normative ranges for particular populations (e.g., patients with chronic kidney disease).
- Intact (second-generation) and bioactive (third-generation) PTH assays are currently used in routine clinical and surgical practice. Fragment-specific assays may increasingly provide insight into the relative contribution of PTH and its fragments to mineral homeostasis in normal and pathophysiological conditions.
- Results obtained by intact and bioactive PTH assays are highly correlated, and both assays can be used for the diagnosis and monitoring of hyperparathyroidism and renal bone disease. The combination of results obtained from intact and bioactive PTH assays may aid in diagnosing parathyroid carcinoma.
- Clinicians and surgeons must always be aware of the particular assay being used and the normal values that are associated with their use.

Expert Opinion

The evolving utilization of intraoperative PTH testing has served as an invaluable and cost-effective tool in parathyroidectomy. A thorough understanding of the clinical chemistry involved with intraoperative PTH analysis, as well as an understanding of pre-analytical and practical testing considerations, contributes to optimization of clinical practice.

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Parathyroid Coding and Billing

43

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Contents

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Introduction

The goal of this chapter is to make coding and billing for parathyroid services understandable and applicable for physicians, who are not traditionally trained in healthcare policy or practice management infrastructure (Fig. 43.1). Clinical and operative parathyroid codes are provided for easy reference, along with expert commentary outlining their appropriate use. Charts and tables are provided to increase documentation precision (not volume) and coding accuracy.

ICD-9-CM/ICD-10-CM

The USA is scheduled to adopt the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) on October 1, 2015. The new code set has over 50,000 more codes than ICD-9-CM. ICD-9-CM to ICD-10-CM translations are not always 1:1 and should be understood as approximations. Diagnosis code(s) should support the Current Procedural Terminology® code(s) billed. Pertinent ICD-9-CM codes are listed next to the equivalent ICD-10-CM code in parentheses below.

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252.01 (E21.0)—Primary hyperparathyroidism
227.1 (D35.1)—Benign neoplasm parathyroid gland [e.g., adenoma]
Example: For a resection of a parathyroid adenoma (CPT 60500), the primary diagnosis code is 227.1 (035.1) and 252.0 (E21.0) is a secondary diagnosis code.

194.1 (C75.0)—Malignant neoplasm, parathyroid gland
252.02 (E21.1)—Secondary hyperparathyroidism, non-renal
252.08 (E21.2)—Other hyperparathyroidism, tertiary hyperparathyroidism
259.3 (E34.2)—Ectopic hormone secretion, not elsewhere classified
Ectopic: Antidiuretic hormone secretion [ADH], hyperparathyroidism
255.10 (E26.9)—Hyperaldosteronism, unspecified
268.2 (M83.9)—Osteomalacia, unspecified
268.9 (E55.9)—Unspecified vitamin D deficiency, unspecified, avitaminosis D
268.0 (E55.0)—Active rickets
275.2 (E83.40)—Disorders of magnesium metabolism, hypermagnesemia, hypomagnesemia
275.3 (E83.30)—Disorders of phosphorous metabolism, familial hypophosphatemia, hypophosphatemia, vitamin D-resistant: osteomalacia, rickets
275.42 (E83.52)—Hypercalcemia
275.5 (E83.81)—Hungry bone syndrome

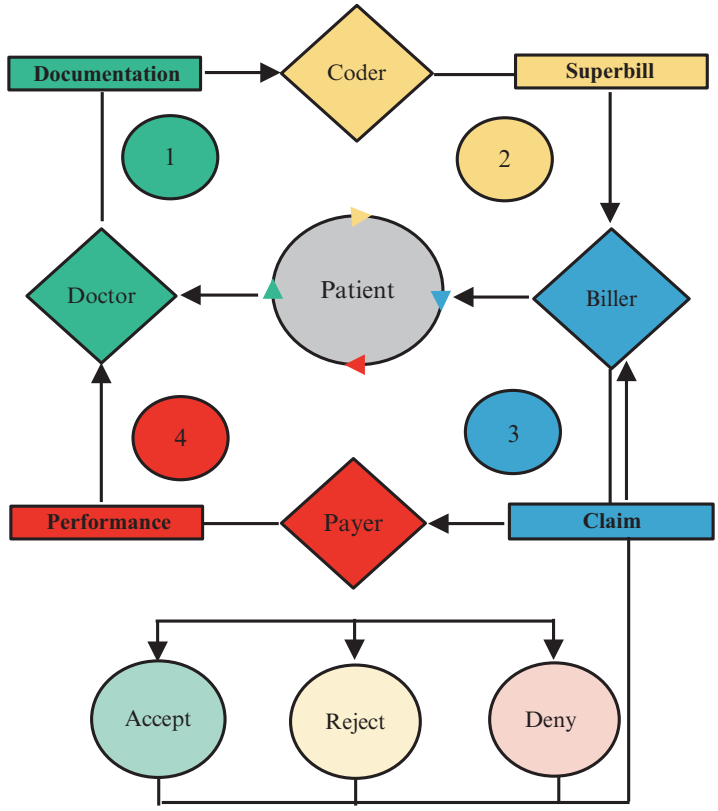

Fig. 43.1 A general overview of the reimbursement cycle. A physician documents the services and procedures provided along with their medical indications. This information is consolidated into diagnosis (ICD-9-CM/ICD-10-CM[1]) and CPT[2] (current procedural terminology) numeric codes such as those for evaluation and management (E/M) and surgical services. The practice's biller transmits the codes via a claim to the payer. After evaluating the claim, the payer returns the claim, in an explanation of benefits (EOB) format, to the practice. The patient is then notified for any and all remaining costs, when appropriate. The biller is responsible for monitoring payment status and ensuring timely and appropriate compensation. Original graphic

278.4 (E67.3)—Hypervitaminosis D
579.0 (K90.0)—Celiac disease
585.9 (18.9)—Chronic kidney disease, unspecified
586 (N19)—Renal failure, unspecified
588.81 (N25.81)—Secondary hyperparathyroidism (renal origin)
592.0 (N20.0)—Calculus of kidney (e.g., kidney stones)
733.90 (M89.9/M94.9)—Disorder of bone and cartilage, unspecified
733.93 (M84.36-)—Stress fracture of tibia or fibula (additional characters change depending on type of encounter and laterality of tibia or fibular—refer to ICD-10-CM resource)
781.7 (R29.0)—Tetany
791.9 (R82.99)—Other nonspecific findings on examination of urine (e.g., hypercalciuria)

Pertinent CPT Codes for Parathyroid-Related Services

The CPT codes pertinent to non-office visit parathyroid-related services include, but are not limited to, the codes listed below. The first two codes, 60500 and 60502, are the two most common codes used by parathyroid surgeons.

60500—Parathyroidectomy or exploration of parathyroid(s)
60502—Parathyroidectomy or exploration of parathyroid(s); re-exploration
31575—Laryngoscopy, flexible fiber optic; diagnostic
31599—Unlisted procedure, larynx [use for procedures that do not have a CPT code such as vocal cord medialization. Refer to CPT 2017 for a new CPT code for this procedure.]
60505—Parathyroidectomy or exploration of parathyroid(s); with mediastinal exploration, sternal split, or transthoracic approach
+60512—Parathyroid autotransplantation (List separately in addition to code for primary procedure)
60520—Thymectomy, partial or total; transcervical approach (separate procedure)
60521—Thymectomy, partial or total; sternal split or transthoracic approach, without radical mediastinal dissection (separate procedure)
60699—Unlisted procedure, endocrine system
76536—Ultrasound, soft tissues of head and neck (e.g., thyroid, parathyroid, parotid), real time with image documentation
78808—Injection procedure for radiopharmaceutical localization by non-imaging probe study, intravenous (e.g., parathyroid adenoma) [for example, radiopharmaceutical probe localization, intravenous injection]
83970—Parathormone (parathyroid hormone) [for example, PTH (C-terminal, intraoperative, intact, etc.]
+95940—Continuous intraoperative neurophysiology monitoring in the operating room, one-on-one monitoring requiring personal attendance, each 15 min (List separately in addition to code for primary procedure)
+95941—Continuous intraoperative neurophysiology monitoring, from outside the operating room (remote or nearby) or for monitoring of more than one case while in the operating room, per hour (List separately in addition to code for primary procedure)

Modifiers

Modifiers are two-digit codes that are appended to a CPT code and provide more information to a payer about the code(s) reported. The most common modifiers used for parathyroid-related services are:

22—Increased procedural services: Use when the physician work required providing a service is substantially greater than typically required to provide the service. Documentation must support the substantial additional work and the reason for the additional work (i.e., increased intensity, time, technical difficulty of procedure, severity of patient's condition, physical and mental effort required). This modifier should be appended to a procedure code and not an Evaluation and Management (E/M) code.
26—Professional component: Use when reporting a radiology CPT code (e.g., 76536) and

the physician provides only the radiological supervision and interpretation (S&I) portion of the service. The facility, or entity, that owns the equipment will report the radiology CPT code with modifier TC (technical component).

51—Multiple procedures: When multiple stand-alone procedure codes are performed at the same session by the same provider, the secondary lower valued procedure(s) may be identified by appending modifier 51. This modifier should not be appended to designated add-on codes such as 60512 (parathyroid autotransplantation) which are noted in CPT by the "+" symbol just prior to the code. Typically payers apply a multiple procedure payment reduction (MPPR) when modifier 51 is used; Medicare's payment is reduced by 50% for overlapping pre-, intra-, and postoperative care.

59—Distinct procedural service: Occasionally it may be necessary to indicate that a procedure or service was distinct or independent from other non-E/M services performed on the same day. To support modifier 59, documentation must indicate that a different session, different procedure or surgery, different site or organ system, separate incision or excision, separate lesion, or separate injury (or area of injury in extensive injuries) not ordinarily encountered or performed on the same day actually was performed by the same individual. Use modifier 59 if another more descriptive modifier is not appropriate and the use of modifier 59 best explains the circumstances.

Evaluation and Management (E/M) Services and Supporting Documentation [2] (Refer to Tables 43.1, 43.2, 43.3, 43.4, 43.5, 43.6, 43.7, and 43.8)

Evaluation and Management codes are codes for nonsurgical services typically performed in the office and/or hospital setting. These codes may be used by a physician or other qualified healthcare professionals such as a non-physician practitioner (NPP) including a physician assistant or nurse practitioner. E/M codes and their associated documentation guidelines are defined by CPT as well as Medicare (Fig. 43.2).

Table 43.1 Progression of the elements required for each type of history

I. HPI	II. ROS	III. PFSH	IV. Type of history
Brief	N/A	N/A	Problem focused
Brief	Problem pertinent	N/A	Expanded problem focused
Extended	Extended	Pertinent	Detailed
Extended	Complete	Complete	Comprehensive

Adapted from 1997 Documentation Guidelines for Evaluation and Management Services; American Academy of Otolaryngology Head and Neck Surgery
To qualify for a given type of history, all three elements in the table must be met. A chief complaint is always indicated. *HPI* history of present illness, *ROS* review of systems, *PFSH* past family/social history

Table 43.2 Brief versus extended history of present illness (HPI)

I. HPI type	Description
Brief	Describe one to three elements of the HPI
Extended	At least four elements of the HPI, or the status of at least three chronic or inactive conditions

Adapted from 1997 Documentation Guidelines for Evaluation and Management Services; American Academy of Otolaryngology Head and Neck Surgery

Table 43.3 Review of systems

II. Review of systems
Constitutional
Eyes
Ears, nose, mouth, throat
Cardiovascular
Respiratory
Gastrointestinal
Genitourinary
Musculoskeletal
Integumentary
Neurological
Psychiatric
Endocrine
Hematologic/lymphatic
Allergic/immunologic

Adapted from 1997 Documentation Guidelines for Evaluation and Management Services; American Academy of Otolaryngology Head and Neck Surgery

Table 43.4 Review of systems (ROS)

ROS	Description
Problem pertinent	Positive responses and pertinent negatives for the system related to the problem should be documented
Extended	The patient's positive responses and pertinent negatives for two to nine systems should be documented
Complete	At least ten organ systems must be reviewed. Those systems with positive or pertinent negative responses must be individually documented. For the remaining systems, a notation indicating all other systems are negative is permissible. In the absence of such a notation, at least ten systems must be individually documented

Adapted from 1997 Documentation Guidelines for Evaluation and Management Services; American Academy of Otolaryngology Head and Neck Surgery

Frequently Asked E/M Clinical Questions

1. *What are the criteria for a new versus established patient?*

   A new patient has not been seen by the same specialty (e.g., otolaryngology) in the same group or practice (i.e., **same tax identification number**) within the **last three years**.
2. *What are the differences between the required documentation components for a new versus established patient?*

   For a **new patient** (99201–99205) all **three of the three key components** (history, exam, medical decision making) are required to qualify for the level of care selected. The code is determined by the lowest of any of the three

Table 43.5 General multi-system exam

System/body area	Elements of general multi-system exam (1997)
Constitutional	• Three vital signs (BP, pulse, RR, T, Ht, Wt) • Appearance
Eyes	• Conjunctivae and lids • Pupils and irises • Optic discs and posterior segments (ophthalmoscope)
Ears, nose, throat, mouth	• Ears and nose (external) • External auditory canals and tympanic membranes (otoscope) • Hearing • Nasal mucosa, septum, and turbinates • Lips, teeth, and gums • Oropharynx
Neck	• Neck • Thyroid
Respiratory	• Respiratory effort • Percussion of chest • Palpation of chest • Auscultation of lungs
Cardiovascular	• Palpation of heart • Auscultation with notation of abnormal heart sounds or murmurs • Carotid arteries • Abdominal aorta • Femoral arteries • Pedal pulses • Extremities for edema and/or varicosities
Chest	• Inspection of breasts • Palpation of breasts and axillae
Abdomen	• Examination of abdomen • Examination of liver and spleen • Examination for the presence or absence of hernia • Examination of anus, perineum, and rectum • Obtain stool sample for occult blood test

(continued)

Table 43.5 (continued)

System/body area	Elements of general multi-system exam (1997)
Genitourinary	• Examination of the scrotal contents (male) • Examination of the penis (male) • Digital rectal examination of prostate gland (male) • External genitalia and vagina (female) • Urethra • Bladder • Cervix (female) • Uterus (female) • Adnexa/parametria (female)
Lymph Nodes	• Palpation of lymph nodes in **two or more** areas • Neck • Axillae • Groin • Other
Musculoskeletal	• Examination of gait and station • Inspection and/or palpation of digits and nails Examination of joints, bones, and muscles of **one or more of the following six** areas: (1) head and neck; (2) spine, ribs, and pelvis; (3) right upper extremity; (4) left upper extremity; (5) right lower extremity; and (6) left lower extremity. The examination of a given area includes: • Inspection and/or palpation • Assessment of range of motion • Assessment of stability • Assessment of muscle strength and tone
Skin	• Inspection of skin and subcutaneous tissue • Palpation of skin and subcutaneous tissue
Neurological	• Test cranial nerves with notation of any deficits • Examination of deep tendon reflexes with notation of pathological reflexes • Examination of sensation
Psychiatric	• Description of patient's judgment and insight Brief assessment of mental status including: • Orientation to time, place, and person • Recent and remote memory • Mood and affect

Adapted from 1997 Documentation Guidelines for Evaluation and Management Services; American Academy of Otolaryngology Head and Neck Surgery
BP blood pressure, *RR* respiratory rate, *T* temperature, *Ht* height, *Wt* weight

Table 43.6 Level of exam

Level of exam	Perform and document
Problem focused	**One to five** elements identified by a bullet
Focused	**At least six** elements identified by a bullet
Detailed	**At least 2** elements identified by a bullet **from each of the 6 areas/systems** OR **at least 12** elements identified by a bullet **in 2 or more areas/systems**
Comprehensive	Perform **all elements** identified by a bullet in **at least nine** organ systems/body areas and document **at least two** elements identified by a bullet **from each of the nine areas/systems**

Refer to the guidelines for other organ system-specific exams such as the ears, nose, mouth and throat exam as well as the hematologic/lymphatic/immunologic exam
Adapted from 1997 Documentation Guidelines for Evaluation and Management Services; American Academy of Otolaryngology Head and Neck Surgery

Table 43.7 Medical decision making

Reviewed data	Points
Review and/or order of clinical lab tests	1
Review and/or order of tests in the radiology section of CPT	1
Review and/or order of tests in the medicine section of CPT	1
Discussion of test results with performing physician	1
Decision to obtain old records and/or obtain history from someone other than the patient	1
Review and summarization of old records and/or obtaining history from someone other than the patient and/or discussion of case with another healthcare provider	2
Independent visualization of image, tracing, or specimen itself (not simply review of report)	2
Total	

Column A	B × C = D		
Problem(s) status	Number	Points	Total
Self-limited or minor (stable, improved, or worsening)	Max = 2	1	
Established problem (to examiner); stable, improved		1	
Established problem (to examiner); worsening		2	
New problem (to examiner); no additional workup planned	Max = 1	3	
New problem (to examiner); additional workup planned		4	
Total			

Multiply column B times column C to equal column D. Enter the column D score into the second row of the Medical Decision Making table

The audit tool used by Medicare, and most private payers, assigns a point value for key elements such as data review and patient problems. The relevant tables are shown below but readers should also refer to CMS guidelines

Table 43.8 Level of risk[a]

Level of risk	Presenting problem	Diagnostic procedures	Management
Minimal	Common cold	Routine labs, imaging	Rest
Low	1 (stable chronic illness)	Imaging studies (non-cardiovascular with contrast)	OTC drugs, PT/OT, IVFs
Moderate	>1 (stable chronic illness) OR 1 (progressing illness)	Imaging studies (cardiovascular) with contrast, cardiac catheterization	Prescription drug, elective major surgery with no risk factors
High	One or more chronic illnesses with severe exacerbation, progression, or side effects of treatment	Cardiovascular imaging studies with contrast with identified risk factors	Elective major surgery (open, percutaneous, or endoscopic) with identified risk factors Emergency major surgery (open, percutaneous, or endoscopic)

Adapted from 1997 Documentation Guidelines for Evaluation and Management Services; American Academy of Otolaryngology Head and Neck Surgery. OTC over the counter, PT/OT physical therapy/occupational therapy

[a]Note that the risk table is only intended to offer examples and readers should refer to the official CMS guidelines for more specific criteria governing risk classification

components. For an **established patient** (99212–99215), only **two of the three key components** must be met to qualify for a particular code level. The code is generally determined by the highest value of the two components selected though the medical necessity for performing the level of the components must be justified.

3. *Can an otolaryngologist bill for a mirror exam using the indirect laryngoscopy code (31505)?*

No. This is part of the ENT exam and not separately reported.

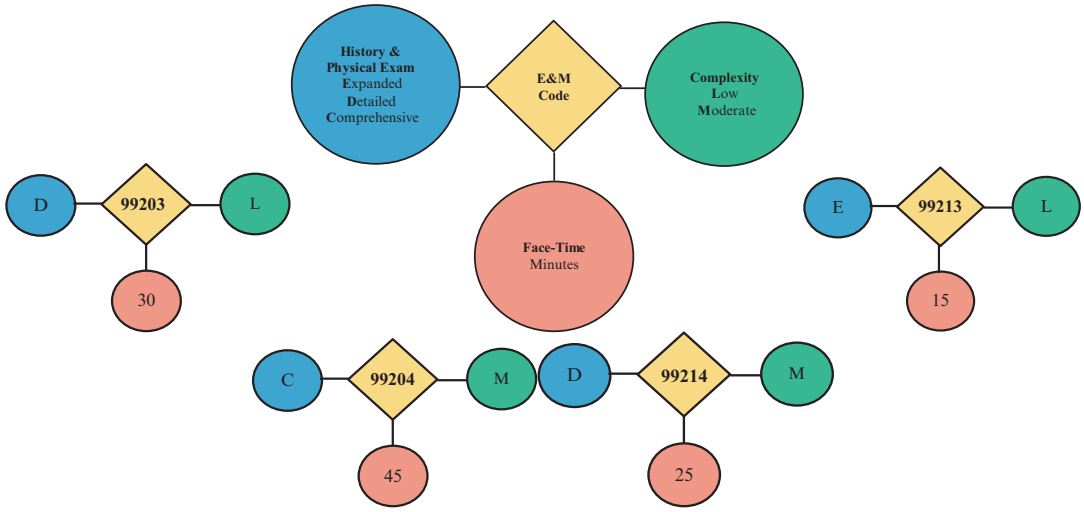

Fig. 43.2 Required E/M documentation components. Level 3 (99203, 99213) and Level 4 (99204, 99214) E/M codes are commonly used for parathyroid clinical visits. The three components of E/M documentation include the history (*BLUE*), physical exam (*BLUE*), and medical decision making (MDM; *GREEN*). The history and exam are further classified according to the required amount of data required for documentation: problem focused (*P*) expanded problem focused (*E*), detailed (*D*), or comprehensive (*C*). Similarly, MDM is classified as straightforward (*S*), low (*L*), moderate (*M*), or high (*H*) complexity. Face-to-face time (*RED*) with the patient may be the sole determining factor if ≥50% physician-patient face-to-face time is spent counseling the patient AND time criteria for the code is met

4. *A patient with recurrent hyperparathyroidism complains of persistent hoarseness. Can an otolaryngologist bill for a flexible fiber-optic laryngoscopy (31575) using modifier 25 for an E/M visit?*

   It depends. All minor procedure codes, such as the flexible fiber optic laryngoscopy (FFL), include an E/M service on the day of the procedure. In order to report 9921x-25 and 31575 there should be documented a significant and separately identifiable E/M service as well as the procedure. Both services can be within the same clinical visit note or the services can be on separate notes. Modifier 25 means that a provider has gone "above and beyond" what is included in the procedure code (all CPT codes have inherent E/M components). A different diagnosis is NOT required for minor procedures (0 or 10 global days) but the medical necessity for separately reporting an E/M code should be justified in the note; in other words, both notes should stand alone as separate necessary services.
5. *If a patient presents on the morning of surgery and the H&P is expired, can a surgeon use modifier 57 on an E/M code to report the H&P the morning of the parathyroidectomy?*

   No. Do NOT use modifier 57 on an E/M code to report a routine pre-op visit or an H&P on the day of (or day before) an elective procedure. These visits are included in the global surgical package. Modifier 57 is for demonstrating that a go-to-surgery decision was made the day of or day before a major procedure (postoperative global period of 90 days). Such emergent surgery is not relevant for parathyroid surgery.

Surgical Codes and Supporting Documentation

Parathyroidectomy (60500-60505)

1. *Indications*—symptomatic primary hyperparathyroidism (pHPT); asymptomatic pHPT with hypercalcemia, hypercalciuria, decreased creatinine clearance, nephrolithiasis, young age, and osteoporosis; medical refractory secondary hyperparathyroidism.

2. *Definition*—exploration and potential resection of one or more parathyroid glands.
3. Parathyroidectomy/exploration (60500) (90-day global)—standard, all-encompassing code for resection of one or more parathyroid glands. The procedure can only be reported once independent of the number of glands resected. Use 60502 for re-exploration. Use 60505 when a sternal split or transthoracic approach is required. Do NOT use modifier 50 to indicate bilateral exploration and/or resection.
4. Parathyroid autotransplantation (60512)—This is an add-on code, which is listed separately in addition to code for the following primary procedures: 60500, 60502, 60505, 60212, 60225, 60240, 60252, 60254, 60260, 60270, and 60271. Following removal of all parathyroid glands, the surgeon may dissect normal parathyroid tissue into millimeter slices and implant the tissue into the sternocleidomastoid, forearm muscle, or another location. Parathyroid autotransplantation is considered investigational ONLY when done as a separate stand-alone procedure. If this is the case, use 60699 (unlisted procedure, endocrine system) instead of 60512. Parathyroid autotransplantation is usually not necessary with a thyroid lobectomy (60200, 60210, 60220); thus, these codes are not listed by CPT as primary procedure codes applicable to the add-on code 60512.
5. *Operative Techniques*
   (a) **Intraoperative PTH assay** (**36500**, **60500**)—(venous catheterization for selective organ blood sampling for multiple intraoperative PTH draws, intraoperative PTH). CPT 36500 is a one-time charge regardless of the number of blood draws and assays performed if performed by another provider (e.g., anesthesiologist). This is not billable for the surgeon.
   (b) **Radio-guided parathyroidectomy**—(78808) (injection procedure for radiopharmaceutical localization by non-imaging probe study, intravenous (e.g., parathyroid adenoma) is considered an "incident to" service). This means that the physician, working in a hospital setting, is not entitled to payment for professional services by Medicare if the physician does not personally perform the service (e.g., supervision alone does not constitute a reimbursable practitioner service). Modifier 26 (professional component) does NOT apply to this code. See individual non-Medicare payer policies for exceptions.
   (c) **Intraoperative ultrasonography** (**US**)—(76998) Intraoperative US guidance is not billed separately in either thyroidectomy or parathyroidectomy because it is included in the global surgical package for the surgeon. A radiologist may separately report the code.
   (d) **Methylene blue injection**—Methylene blue injection is not a recognized procedure code and the respective HCPCS code (A9535) was removed in 2010.
   (e) **Intraoperative nerve monitoring** (+95940, +95941)—There is not a code for reporting surface electrode EMG monitoring for recurrent laryngeal nerve monitoring during thyroid or parathyroid surgery as this is included in the global surgical package for the surgeon. Intraoperative nerve monitoring (IONM) add-on codes (95940, 95941) are not billed separately unless a qualified provider is solely dedicated to the service [3].
   (f) **Endoscopic**, **video-assisted**, **and/or robotic parathyroidectomy** (S2900, 60699)—Significant advances have been made in the diagnosis and treatment of hyperparathyroidism, and codes frequently do not exist for the procedure performed. Reimbursement in the above cases depends on the use of an unlisted code for the entire procedure or perhaps appending modifier 22 to an existing CPT code for the procedure performed. S2900 is an HCPCS II code that may be reported as an add-on code by the surgeon for use of the robot; however, most payers do not separately reimburse the surgeon for use of this technology.

Summary

There is a general tendency for physicians to overcode new patients and undercode established patients. Parathyroid specialists should not automatically equate "routine" or "familiar" with low-level E/M services. Instead it is important to become familiar with the various E/M components and use customized templates to increase efficiency and minimize errors. CPT 60500 is an all-encompassing code for exploration and potential resection of one or more parathyroid glands and may be reported once per operative session, independent of the number of glands resected. If a parathyroid adenoma is resected, the primary diagnosis code is 227.1/D35.1 (parathyroid adenoma), and primary hyperparathyroidism (252.02) is a secondary diagnosis. Autotransplantation of a parathyroid gland during the course of a partial or total thyroidectomy can be appended with modifier 22 or the add-on code 60512. Parathyroid autotransplantation is reported as the add-on code 60512 after parathyroidectomy but this code is never reported as an independent procedure.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion

- The goal of this chapter is to increase documentation precision to support the medical necessity of the service provided and code billed-NOT increase volume (number of codes).
- **Complexity is defined by CPT and CMS—not the physician's experience**. Parathyroid specialists should not automatically equate "routine" or "familiar" with a low medical decision making.
- Independently reviewing and documenting as "my review of the parathyroid scans shows …." (despite an official radiology report) improves patient care and earns 2 data points per Medicare's E/M audit tool.
- Documenting *"Imaging was reviewed"* however earns 0 points. You must briefly detail your personal findings to earn two points.
- Endocrinology (46), otolaryngology (04), and general surgery (01) are distinct CMS-recognized specialties. A patient is "new" for each physician, even if working in the same office/center (tax ID).
- Autotransplantation of a parathyroid gland **during the course of thyroid lobectomy can be billed with modifier 22** because the two parathyroids associated with the remaining lobe are typically not at risk. Parathyroid autotransplantation (60512) **after total parathyroidectomy should be used as an add-on code with 60500**.

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Large Databases for Health Services Research in Endocrine Surgery

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Introduction

Every day, billions of people worldwide contribute to the collection of big data. They use mobile phone applications, receive medications from pharmacies, interact on social websites, and visit medical clinics and emergency departments [1]. These daily activities are responsible for the massive influx of electronic data on a scale of petabytes [2]. With the use of complex statistical schemes and sophisticated computer programming, this information is harnessed into workable databases and used by researchers around the globe [3]. In the United States, we have seen the end-products of research using large databases by groups such as the National Security Agency, Google, and recent presidential campaigns [4]. Health service researchers are particularly well-positioned to use large biomedical databases in order to answer clinically relevant questions that previously necessitated the format of an expensive and resource-intensive randomized controlled trial (RCT) [5].

The Health Information Technology for Economic and Clinical Health (HITECH) Act, made law in 2009 as part of the economic stimulus package, provided 27 billion dollars over 10 years for the widespread adoption of electronic health records (EHRs) in the US [6, 7]. The Center for Medicare and Medicaid Services thereafter linked reimbursement to medical facilities' successful

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adoption of EHR technology, including all of the tenets of the "meaningful use" regulation [8]. Led by financial incentives, adoption of EHRs multiplied within 2 years following HITECH legislation [9]. Between the adoption of EHRs and the rise of health-related social networking, electronic collection of patient data has continued to experience a significant surge in growth [5]. Data entry is occurring at unprecedented rates in both provider-controlled clinical and administrative databases as well as in recently developed patient-controlled health records.

Opportunities for health services research using large databases abound. This research is facilitating the development of new knowledge regarding the natural history of disease, outcomes of specific patient populations, effectiveness of medical and surgical interventions, and their interplay in the modern healthcare milieu [2]. Indeed, the field of comparative effectiveness research was born in this era of large biomedical databases [2]. Important clinical questions are being answered quickly with millions of data-points from patients in real-world settings [9–11]. The velocity with which data is collected, stored, and analyzed far surpasses that of other research modalities in medicine [12]. Furthermore, although establishment and implementation of EHRs have not been without significant initial costs, the efficiency with which health services research is conducted using large databases and the cost-savings realized from changes substantiated by this research are not to be understated [3].

Research with large, publicly available databases is providing new insights into treatment effects and comparative effectiveness, but their use has several limitations. With the volume, velocity, and variety of available data comes potential for low quality and enough ambiguity to render the available data meaningless and possibly invalid [2, 11–13]. Administrative databases built on data entry by trained medical coders might feature errors secondary to manual data entry, inaccuracies because of inadequate codebooks, and the potential for missing information. These problems are not unique to administrative databases, as clinical databases structured around unstandardized input from often rushed providers also present problems for pursuit of well-conducted research [2]. Some have argued that collection of patient data also increases risk of patient privacy breaches and ignores fundamental considerations of patient autonomy in deciding how their health information is to be used [14]. Additionally, lack of randomization increases risk of selection, confounding, and measurement biases, ultimately heightening the potential for misguided research conclusions [11].

In spite of the drawbacks of large databases, their benefit for health services research is still considerable, provided the research is rigorously performed and conclusions drawn from these studies are evaluated with a critical eye. One must consider the quality of the data, the appropriateness of the statistical methods, and the prudence with which conclusions are made [3]. If performed and evaluated discerningly, the potential for use of large databases in health services research is nearly limitless. Many opportunities exist for researchers in the field of endocrine surgery. From understanding the nuanced epidemiology and treatment of thyroid cancer to determining survival impact of treatments for hyperparathyroidism, and various clinical concerns in between, the field of endocrine surgery continues to evolve because of large database research [15–18].

This chapter will describe nine large databases that may be useful for health services research related to endocrine surgery. For each database, we will describe the source of the data, the outcomes available, known limitations in their application, and examples of research questions addressed using them. With these aspects detailed in the following pages, we anticipate that researchers and clinicians alike will gain insight into the utility and appropriateness of performing endocrine surgery research with the large databases identified.

National Safety Quality Improvement Program

The National Safety Quality Improvement Program (NSQIP) was initiated by the American College of Surgeons (ACS) (https://www.facs.org/quality-programs/acs-nsqip). ACS NSQIP

provides a nationally validated, risk-adjusted, outcomes-based program to measure and improve the quality of surgical care [19]. The roots of the ACS NSQIP program are based in the Veterans Affairs Hospital system. In the early 1990s, scrutiny over the quality of surgical care in VA hospitals gave way to the need for risk-adjusted models to account for surgical outcomes (e.g. operative mortality and complications) and comparisons to national averages. As no such estimate of risk-adjusted national averages existed, given the infrastructure of the VA system, they realized they were in a unique position to create these models. Ultimately, risk models for 30-day mortality and morbidity in nine surgical specialties were created.

Over time, with comparative assessment of outcomes, quality improvement was initiated at VA hospitals with a consequent 47 % drop in postoperative mortality, as well as a 43 % drop in morbidity rates, from 1991 to 2006. In 1999, the private sector became interested in NSQIP, and sought to replicate the success of the VA risk-adjustment models, taking into account the more heterogeneous private sector population. In 2001, ACS launched a pilot program funded by the Agency for Healthcare Research and Quality (AHRQ) to improve the care of surgical patients in the private sector. This pilot program of 18 private sector hospitals was a success, and in October of 2002, the Institute of Medicine named NSQIP the "best in the nation" for measuring and reporting surgical quality and outcomes.

In 2004, the ACS began enrolling additional private sector hospitals into the program and became the first nationally validated, risk-adjusted outcomes-based program to measure and improve the quality of surgical care across surgical specialties in the private sector. Today, the program includes 600 hospitals and growing. The ACS NSQIP program operates in 49 of the 50 states and over 50 hospitals in nine countries. In addition to the Healthcare Cost and Utilization Project-National Inpatient Sample (HCUP-NIS), NSQIP serves as one of the major sources to benchmark thyroid and parathyroid outcomes.

The ACS NSQIP includes patients at least 18 years of age and older. Data from patient charts is abstracted by a trained clinical reviewer using validated definitions to ensure accuracy and reliability. National data are accessed through a Health Insurance Portability and Accountability Act (HIPAA)-compliant participant use data file (PUF).

ACS NSQIP collects a diverse array of outcomes, which are often used as quality metrics for surgical care. In contrast to other databases rooted in 30-day post-discharge outcomes, outcomes in NSQIP are based on the 30 days following the index surgical procedure. Traditional outcome measures such as mortality and length of stay are measured. A wide host of postoperative complications, which include surgical site infections, pneumonia, thromboembolic events, urinary tract infections, cerebrovascular accidents, failure to wean off of the ventilator in 48 h, and acute renal failure, are captured by clinical reviewers. The clinical reviewer also collects information regarding presence of diagnoses on admission, thereby allowing for more accurate and reliable representation of the data. Other tracked outcomes include interval from procedure to complication, operative duration, return to the operating room, and discharge destination such as skilled nursing facilities, acute care, or rehabilitation centers. Additional metrics of quality which have received recent attention such as readmission, unplanned and planned, and unplanned return to the operating room (OR) were added to the data collection process in 2011.

As ACS NSQIP was founded on the principle of risk adjustment, the database contains a large number of covariates. Basic demographic data including age, sex, and race/ethnicity is collected. ACS NSQIP includes both distinct preoperative conditions, as well as patient comorbidities. The NSQIP uses its own set of preoperative conditions and comorbidities collected by a trained surgical clinical reviewer.

Comorbidities captured include chronic obstructive pulmonary disease, peripheral vascular disease, coronary artery disease, hypertension, congestive heart failure, and diabetes. Assessment of preoperative conditions includes receipt of preoperative transfusions, chemotherapy, weight loss, steroid use for chronic conditions, and radiation therapy. Many of these variables are determined within a 30-day interval

before the procedure, but some comorbidities (e.g. receipt of radiation therapy) are tracked for up to 90 days prior to the index procedure. Information about smoking status, alcohol use, functional status (e.g. independent, partially dependent, totally dependent), and "do not resuscitate" (DNR) orders is also available. Also, preoperative laboratory values are available such as sodium, creatinine, albumin, and bilirubin, with occasionally available data on temporal relationship to index procedure.

Admission-related characteristics such as inpatient/outpatient status and transfer status are collected. Unique operation-related variables are captured, including surgical specialty of primary surgeon, presence of residents in the OR with corresponding post-graduate year (PGY) of training, elective/urgent/emergent nature of procedure, principle anesthesia technique utilized, intraoperative transfusions, wound classification, and duration of operative time. Additionally, codes for concurrently performed procedures are also available, providing a surrogate for operative complexity, as well as changes in operative plan (e.g. laparoscopic converted to open procedure).

The major strength of NSQIP lies in its ability to provide risk-adjusted estimates of quality and outcome metrics. The degree of covariates captured allows for sophisticated multivariate regression models to be created for outcomes of interest. Additionally, the number of perioperative complications captured allows for the assessment of a great number of quality metrics. Because these variables are collected by a trained surgical clinical reviewer who reviews charts with refined variable definitions, consults with the operating surgeons in ambiguous cases, and may attend morbidity and mortality conferences, these variables are considered to be validated and more accurate and reliable than other databases [19]. Because complications are captured post-procedure, NSQIP may capture not only complications occurring within the hospital, but also post-discharge complications, which would otherwise be difficult to differentiate in administrative or claims databases.

NSQIP data are cross-sectional, not longitudinal. It only contains data about the index procedure, and does not allow linkages to follow up care or procedures. NSQIP also lacks information about medications. Additionally, no hospital or surgeon identifiers are available, which makes it impossible to study hospital volume and surgeon volume. Furthermore, insurance status of the patient is not available in the PUF. Finally, given the large sample of variables collected in NSQIP and its heterogeneous populations, procedures, and clinical or care pathways of the represented hospitals, there may be data missing for certain variables such as race or laboratory studies.

NSQIP benefits from a large enrollment of hospitals, making additional data available on a yearly basis. Due to its large accruement of patients, a number of researchers have taken advantage of its sample size to study outcomes in thyroid and parathyroid surgery. This is particularly important since the prevalence of complications following these procedures is generally low. By generating larger sample sizes of adverse events and other perioperative outcomes, more meaningful analyses of risk factors are possible, ultimately facilitating efforts to improve the quality of care for these operations.

Using NSQIP, Gupta et al. determined risk-adjusted estimates of overall 30-day mortality and morbidity following thyroidectomy, parathyroidectomy, or both [20]. They found that 30-day mortality was 0.08, 0.16, and 0.2 %, respectively, while 30-day morbidity was 3.5, 3.02, and 4.04 %, respectively. Others have used NSQIP to understand risk factors associated with readmission, another commonly cited quality metric in thyroid and parathyroid surgery [21]. Mullen et al. estimated readmission rates of 4.1 % following thyroidectomy and 3.8 % following parathyroidectomy. After evaluating predictors associated with readmission, they were able to conclude that discharge within 24 h of operation does not affect the likelihood of readmission and emphasized avoidance of postoperative complications as the most important means to avoid readmission [21]. Additional independent factors associated with readmission included declining functional status, preoperative hemodialysis, malnutrition, and increased ASA class.

Some authors have used NSQIP to more closely examine particular postoperative complications in thyroid and parathyroid surgery. For example, Gupta et al. determined that postoperative respiratory failure was a rare event (0.4 %). They found that patients who developed postoperative respiratory failure had significantly higher odds of mortality and longer length of stay (LOS) compared to those that did not. Development of postoperative respiratory failure was also associated with a number of factors such as dependent functional status, advanced age, as well as combined thyroid and parathyroid surgery [22]. Another study questioned the need for routine application of venous thromboembolism (VTE) pharmacologic prophylaxis in the thyroid and parathyroid surgical population [23]. They found that the risk of postoperative bleeding following these operations was greater than the risk of developing a VTE in this population [23]. Yet in a different study, Kuo et al. chose to focus on predictors of reoperative parathyroidectomy. They found that obesity and higher ASA class were more likely to be associated with need for reoperative parathyroidectomy, the rate of which they determined to be 4.1 %. Kuo et al. did not find any difference in rates of mortality and common postoperative morbidity measures between the initial and repeat parathyroidectomy, though the risk of readmission was greater in the reoperative group [24].

Finally, Monteiro et al. estimated trends and disparities in education between surgical specialties [25]. They found that more thyroid and parathyroid operations were performed with general surgery residents relative to those in otolaryngology (ENT). Furthermore, of cases performed with housestaff, they found that percentages performed with junior residents (PGY1-3), senior residents (PGY4,5), and fellows were 42, 50, and 7 %, respectively, whereas for ENT operations, the percentages were 35, 46, and 16 %, in spite of similar case complexity and outcomes. They concluded that those numbers suggest earlier exposure to endocrine surgery for general surgery residents and that this experience was balanced between resident levels, with minimal effect of fellows.

As these studies highlight, the ACS NSQIP is a rich source of data to study outcomes and quality in thyroid and parathyroid surgery. Given the large number of validated clinical outcomes and covariates available, a wide spectrum of research questions can be addressed, with the significant added benefit of being able to risk adjust outcomes.

The Collaborative Endocrine Surgery Quality Improvement Program (CESQIP)

The Collaborative Endocrine Surgery Quality Improvement Program (CESQIP) is an initiative of the American Association of Endocrine Surgeons (AAES) (https://cesqip.endocrinesurgery.org/) [26]. As CESQIP is the newest database available, and the only one dedicated to the practice of endocrine surgery, it is still in the process of accruing membership and data. Cited goals include providing healthcare providers and patients real-time information for understanding value in the delivery of endocrine surgery, establishing a culture of outcomes tracking, and promoting collaboration between endocrine surgeons.

Collected variables are divided into patient characteristics, disease characteristics, operative details, and both short- and long-term postoperative outcomes. Patient characteristics include comorbidities such as diabetes and hypertension, as well as conditions such as obesity and current smoking status. Family history of thyroid cancer, personal history of neck irradiation, and anterior neck or thyroid/parathyroid surgery are also captured, as are specific anticoagulation medications, and baseline vocal cord dysfunction or preoperative laryngoscopy. Hospital and surgeon identity are securely and anonymously tracked for each patient. Disease characteristics include a number of biochemical and hormonal elements such as 24-h urinary calcium, adrenal vein sampling, bone mineral density, C-peptide levels, chromogranin A levels, gastrin, glucagon, pancreatic polypeptide, and somatostatin. Additionally,

fine needle aspiration (FNA) results and type of imaging obtained (e.g. computed tomography, endoscopic ultrasound, ocreotide scan) are included. Histologic characteristics such as immunostaining, mitotic counts and Ki67 index are also catalogued. Operative details include approach (traditional, video assisted, remote endoscopic), adjunct devices (Harmonic, Ligasure), central or lateral neck dissection, autotransplantation, concomitant thymectomies concomitant, intraoperative parathyroid hormone (PTH) levels, transection of recurrent laryngeal nerves, and surgical pathology. Short- and long-term postoperative outcomes, of which are contained in NSQIP, are captured. Unique outcomes specifically related to endocrine surgery are dysphagia, hematoma requiring evacuation, and fistula, as well as long-term dysphagia, persistent disease, or persistent requirement for calcium or vitamin D, need for tracheostomy, or recurrent disease.

Anticipated strengths of this database primarily relate to data capture relevant to the practice of endocrine surgery. Specific endpoints about indications, comorbidities, and outcomes for thyroid, parathyroid, adrenal, and neuroendocrine pancreas cases will be available. As with all NSQIP efforts, these data will be collected by trained clinical reviewers, allowing for assessment of metrics such as complications, outcomes, resource utilization, and adherence to guidelines. This will empower process improvement by providing rigorous, timely feedback to clinicians about comparative performance, and identify and implement best practices while providing benchmarking to peer institutions for quality improvement [26]. While not currently available, it is anticipated that this database will ultimately provide a wealth of data pertinent to the practice of endocrine surgery for those participating in the program.

MarketScan

The Truven Health MarketScan Databases are claims-based databases that include data detailing clinical utilization, enrollment, and payments for over 200 million patients in the US (https://marketscan.truvenhealth.com/marketscanportal/). Detailed patient data is linked to medical encounter information and claims submitted to over 100 private insurers for inpatient, outpatient, and prescription drug services [27, 28]. With data on patients since 1995, the MarketScan databases represent one of the largest health care claims databases available. Several cohorts are available in the MarketScan databases, including: the Commercial Claims and Encounters (CCAE) Database, the Medicare Supplemental (MDCR), the Health and Productivity Management Database, the Benefit Plan Design Database, the Medicaid Database, the MarketScan Lab Database, and the Hospital Drug Database (HDD).

Within the core databases, which include the CCAE, the MDCR, and the Medicaid databases, available data include inpatient, outpatient, and outpatient pharmacy claims as well as enrollment data from large employers. The CCAE entails information on active employees and dependents, non-Medicare retirees and dependents, and those covered under the Consolidated Omnibus Budget Reconciliation Act (COBRA). The MDCR includes data on Medicare-eligible active and retired employees and their Medicare-eligible dependents from employer-sponsored supplemental plans. The Medicaid database contains information on inpatient, outpatient, and pharmaceutical claims of Medicaid recipients from selected US states [28]. Overall, patient information includes basic demographics and comorbidities, listed as a series of up to 15 International Classification of Disease, 9th edition, Clinical Modifications (ICD-9-CM) codes [29, 30]. Diagnostic, procedural, cost, reimbursement, and out-of-pocket payment information is available. Details specific to outpatient services include information on visits to clinics, emergency rooms, and other outpatient-type settings other than facilities assuming care of discharged patients, such as skilled nursing facilities [27]. With regard to pharmaceutical data, medication name, quantity, amount of medication supplied, and cost per prescription is also available [31]. Thus, MarketScan provides a useful resource for

investigators attempting to study utilization and cost of care for working age, insured individuals. Outcomes addressed in previous publications have included data on sequelae of specific diagnoses or procedures, such as readmissions and their associated costs [31, 32]. MarketScan data have been used in over 500 publications in peer-reviewed journals [33].

There are a few unique advantages to MarketScan data that distinguish it from other administrative data sets. First, it is longitudinal; for the duration of the patient's tenure of employment and enrollment, claims for inpatient, outpatients, and outpatient pharmacy are available. It is possible to follow a patient from an office visit to an inpatient visit to follow-up outpatient care. Second, family members are linked in the data set, which allows researchers to study the implications of treatment and disease on the healthcare utilization of family members. Third, the availability of outpatient pharmacy claims is rare among administrative data sets. The patient volume contained within the 20 years that MarketScan has accumulated data has amounted to information on more than 200 million unique patients. However, if a patient switches employers and both previous and new employers contribute information to MarketScan, the patient will appear as two individuals [27].

Although the databases are rich in treatment and financial information, they lack depth in terms of demographic information, such as race and income, as well as clinical data, such as hospital and surgeon volumes [28, 29, 31]. Additionally, while diagnostic, treatment, and procedural data on each patient might be extensive, it is limited to only those diagnoses, medications, and procedures for which claims were submitted. Therefore, not all comorbidities may have been treated and therefore documented, or may not have otherwise affected reimbursement. Moreover, while submitted claims for medications are available, adherence to prescribed dosing or any consumption of prescribed medications is not [30, 31]. As the database is built around ICD-9-CM and CPT codes, the flaws inherent to coding data and the anticipated anxiety associated with the fast-approaching implementation of ICD-10 accompany the use of MarketScan data [34]. Finally, outcomes are limited to resource utilization and costs, and clinical outcomes such as mortality are not available in MarketScan.

Limitations notwithstanding, the MarketScan database has been successfully implemented in studies of care, treatment, and costs associated with a myriad of surgical pathology, including endocrine surgery. In 2013, Korelitz et al. [33] performed an epidemiologic study of thyrotoxicosis in pregnant women, the use of antithyroid medications, and the adverse effects associated with taking those medications during pregnancy with concomitant thyrotoxicosis. Kulaylat et al. [31] explored a cohort of patients who underwent pancreatectomy or hepatectomy to determine costs associated with their index procedures and postoperative readmissions, in an effort to determine the financial impact of two highly morbid procedures. Encinosa and Hellinger [32] used MarketScan data on adult patients who underwent surgery between 2001 and 2002 to characterize the economic burden of preventable adverse medical events over a 90-day period following index dates of medical error. By using large databases like MarketScan, much can be learned about strategies for, and payment of, patient care in the field of endocrine surgery, particularly in this era of our fast-evolving health care system where concerns regarding appropriate utilization of health care resources and dollars continue to mount.

University HealthSystem Consortium

The University HealthSystem Consortium (UHC) (https://www.uhc.edu/) is one of the largest administrative databases currently available, in which participating institutions and organizations contribute clinical, safety, operational and financial data for purposes of comparative analysis between institutions [35]. Beginning in 1984 as a small collection of academic medical centers, the member-owned and operated consortium has expanded to include over 100 principal members and over 300 affiliated members [36–38]. As a

large collaborative database, UHC's mission is to provide a benchmarking platform for its participating members and to leverage this data in an effort to steer the tide of national health care. Both clinical and operational questions comparing outcomes between institutions may be answered using the UHC database [35].

Within UHC, available databases include the Clinical Database/Resource Manager (CDB/RM), the Core Measures Database, the Operational Database, and the Imperatives for Quality Program. Participants in the CDB/RM include over 90 % of the nation's nonprofit academic medical centers, including both principal academic institutions and their affiliated community hospitals [38, 39]. The CDB/RM entails information on demographics, financial data, and diagnostic, procedural, and hospital course-related information. Basic demographics include age, date of birth, race, sex, and zip code. Although lacking specific covariates for comorbidities, risk adjustment is performed by assignment of a severity of illness and risk of mortality level to each patient, regressed against a "normal" reference population, with assignment of expected probabilities of mortality, length of stay, and costs for each individual [40]. Comorbid conditions considered in this scheme are based on research by Elixhauser et al. [41] and are comprehensive for purposes of risk adjustment [40]. Financial data contained within the CDB/RM encompass total and direct costs, charges, revenue and reimbursements, thereby providing information to support cost studies from a range of relevant perspectives.

Outcomes from inpatient admission data include length of stay, morbidity, readmission rate, risk-adjusted in-hospital mortality, and costs. Length of stay is defined as the duration of time from index procedure to discharge. Readmission is defined as any readmission within 30 days following the date of index procedure. UHC collects only information on in-hospital mortality, and does not report on out-of-hospital deaths.

As mentioned, use of the UHC CDB/RM for health services research in endocrine surgery is strengthened by decades of clinical data from over 110 nonprofit academic medical centers and more than 300 affiliated institutions. Thus, the population for which data is collected is much more inclusive than that found in other databases, such as the Surveillance, Epidemiology, and End Results (SEER) database and the ACS NSQIP [39]. Patient data in the inpatient, and more recently the outpatient, settings are available for analysis. Although specific comorbidities are not available in the database, the complex vendor-provided risk-adjustment model accounts for approximately 30 comorbidities in its algorithm to determine probability of mortality, length of stay, and costs for every patient [40]. Adding to the complexity, UHC's model for predicting risk evolves on an annual basis [35]. This database is limited by its cross-sectional nature, retrospective data collection by coders trained in the use of International Classification of Disease (ICD) and Current Procedural Terminology (CPT) coding, a relative dearth of demographic or pharmaceutical data, and segmentation into clinical, operational, core measures, and quality databases.

In spite of limitations, a number of studies within the field of endocrine surgery have resulted from the analysis of UHC data. Stack et al. [38] established reference data for parathyroid interventions performed in the outpatient setting, the current norm for parathyroidectomies, by studying patient data within UHC between 2005 and 2010. Stack et al. [39] also published reference data for thyroid interventions using UHC data for patients with thyroid pathology diagnosed between 2002 and 2009, looking at patient demographics, procedural indications, complications, length of stay, and costs. Adding to this reference data, Hinson et al. [37] examined trends in the use of robotic technique for thyroid surgery between 2009 and 2013, following introduction and implementation of the da Vinci Surgical Robot for minimally invasive thyroidectomies by South Korean endocrine surgeons in 2007. In a comparison of data on surgical patients from 2009 to 2011 reported to the UHC CDB/RM and the ACS NSQIP, Simorov et al. [35] found significant variation in patient characteristics and outcomes between patients matched between the two databases. They found that overall morbidity

and mortality were greater in NSQIP, whereas wound infections and pneumonia occurred more frequently and length of stay was longer in UHC data. These incongruences, even among identical groups of patients, underscore the intricacies of data collection and statistical modeling unique to each large database.

National Inpatient Sample

The National (formerly Nationwide) Inpatient Sample (NIS) is a large discharge database maintained by the Healthcare Cost and Utilization Project (HCUP) (https://www.hcup-us.ahrq.gov/nisoverview.jsp), a public–private partnership between the Agency for Healthcare Research and Quality (AHRQ) and industry partners [42]. NIS is the largest all-payer database that is publicly available in the US and includes inpatient admissions from 1988 to 2012. Prior to its redesign in 2012, the NIS collected all discharges from 20 sample community hospitals. Beginning in 2012, however, the data collection strategy was changed to collect a sample of discharges from all participating hospitals, not including rehabilitation or long-term acute care hospitals in 44 states. Each year of data contains information from approximately seven million hospital stays. Moreover, the data set includes weights that allow extrapolation to the national level. The ability to study national trends and outcomes is a unique strength of the NIS. The NIS can be used to study outcomes for parathyroid and other endocrine surgeries that require inpatient hospitalization.

The NIS contains information about discharges from inpatient stays at US community hospitals. This has important implications for outcomes research in endocrine surgery. For example, most parathyroid surgeries are performed on an outpatient basis. Therefore, the cases included in NIS may represent a biased subsample since they only include cases treated as inpatients. Many outcomes research studies in endocrine surgery using the NIS combine thyroid and parathyroid surgeries together, which helps define a population where the inpatient stay is relevant [43]. Moreover, the NIS contains both adult and pediatric admissions. Cohorts can be created from the NIS sample based on ICD-9-CM diagnosis and/or procedures codes.

Several outcomes are available in the NIS, including vital status at discharge, length of hospital stay, and charges. In addition, cost-to-charge ratios are available, which allow translation of charges into more meaningful cost measures. When transformed, costs represent estimates of costs to providers. In addition, outcomes can be constructed from ICD-9-CM diagnosis codes. For example, Enomoto et al. used ICD-9-CM diagnosis codes to identify surgical complications, such as urinary tract infection, pneumonia, renal insufficiency, renal failure, cardiac arrest, postoperative sepsis, and deep vein thrombosis [44]. More relevant to endocrine surgery, Dehal et al. used ICD-9-CM codes to identify hematoma as a complication of thyroid and parathyroid surgery [43].

Data in the NIS are primarily from uniform billing forms, which standardize the collection of information about patients [45]. These forms include information demographics (including age, sex, race/ethnicity), payer type, admission type and status, type of hospital, and region of the country. Comorbidities are an important control variable in most outcomes research. These are not available directly in the NIS, but can be gleaned from ICD-9-CM codes. This allows not only the identification of specific comorbidities, but also the creation of comorbidity indices such as have been described by Charlson [46, 47] and Elixhauser [41]. HCUP provides code to compute the comorbidities included in Elixhauser [41, 48]. Prior to 2012 the NIS provided encrypted identifiers for physicians, surgeons, and hospitals. This allowed for the estimation of hospital and surgeon volumes, which have been shown to be important drivers of outcomes in many procedures [49, 50]. With the change in data collection in 2012, however, these identifiers have been removed.

One example of the type of outcomes research in endocrine surgery that can be undertaken using the NIS is a recent study by Noureldine et al., who use the NIS to study racial and ethnic disparities in access to high volume surgeons for

thyroid and parathyroid surgery [51]. Thyroid and parathyroid surgeries performed between 2003 and 2009 were identified using ICD-9-CM procedures codes, yielding a cohort of 106,314 patients. Surgeon volume for these surgeries was found to have a significant impact on outcomes. Furthermore, African Americans were found to have poorer access to higher volume surgeons, which in part contributed to more complications following surgery, longer lengths of stay, and higher mortality. In addition, African Americans had poorer outcomes even when treated by higher volume surgeons. Thus, this study suggests that there are racial disparities in both treatment and outcomes that go beyond access to high quality healthcare providers.

The greatest strengths of the NIS are its very large sample size, which allows the study of even rare disease and uncommon procedures, and its ability to perform extrapolations to the national level. For endocrine surgery, the most important limitation of the NIS is that it is limited to inpatient admissions. Hence, many important surgeries done in an outpatient setting, such as parathyroidectomy, are not included. Another limitation is the lack of clinical detail in the data set, as most clinical variables must be gleaned from ICD-9-CM diagnoses as proxies. The quality of such variables varies between institutions and training of coders, with the limitation that diagnosis codes generally underestimate the underlying conditions [44, 52]. Also, for some conditions identified using diagnosis codes, it may be difficult or impossible to distinguish whether the condition is a comorbidity or a complication since dates are not provided to indicate the preexistence of patient conditions. Finally, while the change in data collection strategy that began in 2012 will make estimates of national trends more accurate, it also removed the ability to study hospital and surgeon volume effects in future years.

State Databases

A number of states have unique databases available, often as the result of legislatively mandated reporting, or statewide hospital collaborative efforts. Examples include the Surgical Care and Outcomes Assessment Program (SCOAP) for the state of Washington, Michigan Surgical Quality Collaborative (MSQC), and the Pennsylvania Health Care Cost Containment Council (PHC4). The SCOAP and MSQC do not contain endocrine surgery procedures, but the PHC4 data do. PHC4 is an administrative database that is the result of legislatively mandated reporting for the state of Pennsylvania (http://www.phc4.org/). The PHC4 is an independent stage agency responsible for monitoring the quality and cost of health care, as well as improving access. This database is built on discharge data populated with ICD-9 diagnosis and procedure codes, and as such, contains data about any number of procedures or diagnoses that can be characterized by an ICD-9 code. Data is available each year to institutions and researchers for a fee.

The PHC4 contains data on patients aged 18 years and older. Additionally, it collects patient information from all third-party payers, distinguishing it from other databases such as Medicare-based databases. Patient data are collected for all hospital discharges occurring in all acute care general hospitals, not including Veterans Affairs Hospitals, in Pennsylvania. There are both inpatient and ambulatory datasets available.

The PHC4 offers a number of pertinent outcome measures. The analysis of these outcome measures are enhanced by the longitudinal nature of the database. As such, while primary reported metrics are usually of outcomes within 30 days of procedures or discharge, the database allows for the possibility of tracking its outcomes longer. Outcomes included in the database includes mortality and 30-day readmission status. Additionally, using the ICD-9 diagnosis codes present, numerous authors have established complications schema that can be applied to estimate the postoperative complications of other procedures. The PHC4 tracks its own category of complications in a field named "unusual occurrence." These include urinary tract, surgical wound, respiratory tract, intravenous, and multiple-type infections, as well as infections undetermined etiology, "other," no nosocomial infection present, and "unknown." Collectively, these outcome measures form the majority of the quality metrics being used by the

Centers for Medicare and Medicaid Services (CMS) to track hospital and physician quality of care. Additional outcomes include metrics for resource utilization such as LOS, discharge status (e.g. home, short-term general hospital, skilled nursing facility, long-term care hospital), as well as total charges for care.

Basic demographic data is available including age, sex, and race. As previously mentioned, insurance or payer information is also available. Up to 16 ICD-9 diagnosis codes are available with the primary diagnosis indicated. As such, a Charlson comorbidity index can be computed to estimate the burden of comorbidities and provide variables for potential risk-adjustment. Other variables allowing for severity adjustment present in PHC4 include "Patient Severity Upon Admission" which is based on the admission severity score submitted by the third-party severity provider on the facilities' behalf, and "Patient Morbidity," a score reflecting the morbidity of illness upon admission.

The PHC4 is able to capture admission type to describe patient acuity. Urgent admissions include those where a patient requires immediate attention for the care and treatment of pathologic disorder. Emergent admissions refer to patients requiring immediate medical intervention as a result of a severe, life threatening, or potentially disabling condition.

As an administrative discharge data set containing a large number of ICD-9 diagnosis and procedure codes, PHC4 data provide the ability to define many cohorts and address many outcomes questions. A unique strength of the PHC4 is its longitudinal nature, which is not a feature of other discharge data sets such as NSQIP and NIS. Not only can readmissions within 30-days be identified, but additional readmissions over the course of the year can also be tracked with reasons for readmission determined. This is all made possible by unique identifiers for patients, surgeons, and hospitals. Furthermore, the unique identifiers allow for the estimation of hospital and surgeon volume for diseases and procedures of interest.

The previously noted flexibility in designing research studies founded on the array of ICD-9 codes available also serves as these databases' main limitation. In contrast to previously described databases such as NSQIP, SCOAP, and MSQC, there is no clinical validation of diagnosis codes against discharge data. Therefore, it can be difficult to differentiate whether a particular ICD-9 code relates to a complication from the current admission, a complication from a previous admission, or a comorbidity of the patient. While PHC4 contains data on charges, this metric does not provide an accurate or reliable assessment of costs, and should not be used to understand the economic impact of various diagnoses or procedures. Cost-to-charges ratios are available, for an additional expense, and may be used to provide an estimate of provider costs [53]. Furthermore, the specialty of surgeons performing the operations cannot be determined. Another notable limitation is that the PHC4 does not capture out of state readmissions. Because of this, it may represent a conservative estimate for metrics such as readmission for certain patient populations, particularly those within proximity to bordering state hospitals. Finally, no data is available with regard to pharmacy medications, or laboratory studies.

Though the PHC4 has not yet been utilized to evaluate outcomes in endocrine surgery, it certainly has that potential, and it has been used to describe a number of outcomes for a variety of procedures. Data provided in the PHC4 has allowed for an estimate of the baseline readmission risk factors associated with readmission following procedures such as colectomy, mastectomy, gastric bypass, and carotid endarterectomy/stenting [54–56]. In colectomies, 14.7 % of patients were readmitted following colectomy in the year 2011 in Pennsylvania. The odds of readmission were negatively influenced by particular diagnosis such as ischemic colitis and inflammatory bowel disease (IBD), increasing number of comorbidities, emergent admissions, and/or the presence of an in-hospital complication [54]. Additionally, surgical-related factors such as low-volume surgeons and construction of ileostomy were associated with increased odds of readmission. Laparoscopic approaches to colectomies were found to be protective against readmission after controlling for acuity of admission and patient comorbidities.

In analysis of mastectomy data, increasing LOS was associated with increased odds of readmission [55]. When comparing carotid endarterectomy and stenting, risk-adjusted readmission rates were 10% and comparable for both approaches [56]. Collectively, data in these studies allowed for greater understanding of the phenomenon of readmissions, which is under great scrutiny as a target for quality improvement, with financial penalties levied for poor performers. Finally, hospital costs for disease processes such as *Clostridium difficile* have been characterized among different hospital types, including rural versus urban, and teaching versus nonteaching detail [53]. Because value is often described as the tradeoff between quality and costs, data available in state databases may provide the necessary information to study value in healthcare. In conclusion, each statewide database has different combinations of strengths and limitations that can be leveraged to answer a variety of research questions in endocrine surgery.

National Cancer Database

The National Cancer Data Base (NCDB) is a cofunded effort by the American Cancer Society and the ACS Commission on Cancer (CoC) to provide a centralized national database of outcomes in oncologic care and to facilitate benchmarking in the management of cancer patients (https://www.facs.org/quality%20programs/cancer/ncdb) [57]. Developed in 1989, the NCDB collects data from over 1,500 CoC-accredited cancer programs in the US, Puerto Rico and the District of Columbia, accounting for over 70% of all incident cancer cases. This includes approximately 85% of thyroid cancer cases [58]. This administrative database serves as a platform to assess trends in oncologic care, compare outcomes between treating facilities, and provide data from which progress can be benchmarked in the management of patients diagnosed with cancer [57, 59, 60].

The NCDB collects coded data on patient characteristics, cancer staging and histology, treatment, and outcomes. Malignant pathology is classified according to International Classification of Diseases for Oncology, Third Edition (ICD-O-3) primary site and histology. Patient characteristics include basic demographics such as age, sex, and race, but also encompass level of education, income, treatment facility, and comorbidities [57]. Comorbidities are represented by Charlson/Deyo scoring, with 15 distinct comorbidity categories described [47, 61]. Risk adjustment is enabled by data on American Joint Committee on Cancer (AJCC) stage of disease. Moreover, treatment data are provided, comprehensively covering receipt and timing of surgery, radiation, and systemic treatment modalities. Outcomes available include 30-day and 90-day postoperative mortality, time in months between diagnosis and last contact or death, and vital status. CoC-accreditation mandates that all programs reach a 90% threshold for follow-up and data entry on living and eligible patients entered into the database in the preceding 5 years [57].

The main strength of the NCDB is its broad scope in tracking oncologic care, for which it receives data from the majority of CoC-accredited cancer centers nationwide, with a wide range of ICD-O-3 tumor types included [61]. Patients are followed longitudinally with many incident cases added annually since 1989 [57, 61]. Although an administrative database built on standardized abstraction and coding methods, the NCDB has been validated for oncological studies and audited at the local and national level [60–62]. The NCDB also has limitations, including a lack of disease- and treatment-specific data including tumor recurrence and disease-specific mortality, lack of financial information and pharmaceutical detail beyond chemotherapeutics, and no information regarding surgeon experience and trainee involvement [58, 61, 63].

Despite these limitations, health services researchers continue to contribute to the current fund of knowledge in oncologic care, with publication using the database in over 350 peer-reviewed publications in the last 25 years [57]. The intent of the American Cancer Society and American College of Surgeons to monitor outcomes and support quality improvement is evident in the research generated within the field of endocrine surgery [60]. Hundahl et al. [59] exam-

ined demographic, stage, treatment, and outcome information on patients with parathyroid carcinoma within the NCDB from 1985 to 1995 to provide descriptive statistics for this patient population. In an update of the Hundahl study, Asare et al. [63] used a cohort of patients in the NCDB also diagnosed with malignant parathyroid pathology from 1985 to 2006 to assess overall survival and associated prognostic factors. After characterizing their cohort by age, sex, tumor size, nodal status, extent of resection, and receipt of radiation therapy, they performed multivariate analysis to determine predictors of survival and, therefore, contribute to knowledge pertaining to the course of parathyroid cancer [59, 63].

The specialty of endocrine surgery has certainly been enriched by studies using data collected by the NCDB for parathyroid cancer, as well as for pathology associated with the thyroid, pancreas, and adrenal glands [58, 61, 62, 64]. The NCDB continues to grow, with a stated agenda to monitor clinical management of cancer patients and to develop audit and feedback tools for the promotion of quality care among cancer programs [57, 60]. Its use for benchmarking outcomes of patients with endocrine malignancy will continue to benefit their ongoing care as the NCDB continues to gather new data and research continues to explore the state of oncologic care in the US.

Surveillance, Epidemiology, and End Results

The Surveillance, Epidemiology, and End Results (SEER) program was developed by the National Cancer Institute (NCI) to report on cancer incidence and survival in the United States (http://seer.cancer.gov/). Data are collected from population-based cancer registries that cover approximately 28 % of the US population. The SEER program collaborates with the North American Association of Central Cancer Registries (NAACCR) to archive data content and ensure compatibility between state registries to allow for data pooling and to improve national estimates. SEER began data collection on January 1, 1973 in select states but now has expanded to cover 20 U.S. areas to be representative of the U.S. population, with information available up to 2012 [65, 66].

The SEER program is the only population-based database that includes comprehensive cancer information such as stage and survival. It includes all patients diagnosed with cancer in the registry areas between 1973 and 2012 with no limitations on age. Demographic information collected include age, race, gender, age at diagnosis, geographical location, and marital status. The main outcome variable included in SEER is survival. Vital status, survival time, and cause of death are collected thus allowing study of overall and disease specific survival.

Detailed cancer specific variables are included in the SEER database making it amenable for the study of different cancer types. Primary tumor locations, tumor morphology, and histology are classified using International Classification of Diseases for Oncology (ICD-O) codes. Additional cancer specific information includes tumor grade, size, laterality, and tumor behavior (benign, carcinoma in situ, malignant, etc.). When applicable, nodal involvement, metastasis, and tumor markers are included. For example, estrogen, progesterone, and HER2 status are available for breast cancer. Most importantly, AJCC staging is included since 2010 and adjusted to the most current staging guidelines. However, adjustments are not available for all cancers included in the database.

Treatment data in SEER describe characteristics of surgery and radiation. Cancer-directed surgery and reconstruction are defined based on the data contained within the site-specific surgery data fields. Data on surgical lymph node evaluation, when applicable, are also available. Of note, information on sentinel lymph node biopsies for breast cancer cases has been removed due to miscoding of this data element. Radiation is defined based on the source (i.e., beam, radioactive implants, etc.) and its sequence with surgery is also identified. The complete data dictionary can be found on the SEER website [67].

As with most administrative databases, SEER has its limitations, the foremost being the lack of information on comorbid health status. Pharmacy and chemotherapy data are not collected, which

may limit studies in which types of treatment are of interest. Additionally, treatment data are only captured within 4 months of diagnosis and information on recurrence or metastasis not found on initial evaluation is lacking. Finally, endocrine surgery data in the data set is limited to thyroid and carcinoid tumors only.

SEER-Medicare

The SEER-Medicare data are an extension of the SEER registry (http://healthcaredelivery.cancer.gov/seermedicare/). The SEER-Medicare data set includes patients from the SEER registry who are covered by fee for service Medicare. In addition to the tumor registry provided in SEER, the SEER-Medicare data also includes all Medicare billing claims for these patients, which opens up new possibilities for outcomes and control variables. The linkage of the SEER and Medicare claims databases was achieved through a collaborative effort between the National Cancer Institute, the SEER registries, and CMS. Linkage was first completed in 1991 and has been updated in 1995, 1999, 2003, 2006, 2009, 2012, and 2014. For each update, successful matches were achieved in 93 % of patients over age 65 between SEER and those enrolled in Medicare [68].

The SEER-Medicare linked database contains information for patients covered by Medicare. Most patients qualify for Medicare due to age, which means that most patients are 65 years or older. However, the data set also contains younger patients who qualify for Medicare, qualifying for reasons such as end stage renal disease. In addition, SEER-Medicare includes a cohort of cancer-free patients made up of a random 5 % sample of Medicare beneficiaries residing in SEER areas. This group can be used for comparative studies between cancer patients and controls, those without cancer diagnoses [69, 70].

Claims files make available information regarding all inpatient and outpatient care the patient receives. These claims provide a nearly complete picture of each patient's medical financial history (inpatient, outpatient, home health, skilled nursing home, and durable medical equipment). Because SEER-Medicare contains both inpatient and outpatient data, treatment history for any given disease is fairly complete. This includes surgery and radiation, which are part of SEER, in addition to cancer-directed therapy such as chemotherapy and pharmaceuticals during the follow-up period.

Outcomes of interest included in SEER-Medicare are much more detailed than the survival data provided by SEER. The linkage with Medicare allows for the study of recurrent tumors, new primaries and adverse effects of treatment during the follow-up. Time from initial diagnosis and treatment to development of recurrence, new primary tumors, and subsequent treatment can also be evaluated. Because the database uses Medicare claims, nearly complete follow-up is obtained.

One example that highlights the value of the claims data in SEER-Medicare data comes from Hollenbeak et al. who studied the incidence of recurrence for differentiated thyroid cancer in the elderly. Although recurrence is not captured in the SEER registry, by searching billing claims more than 6 months after initial treatment, the authors were able to identify patients who received additional I-131, additional imaging studies, and additional surgeries (e.g. completion thyroidectomy) that were frequently used following recurrence. Using these billing claims, they found that after the first 2 years of diagnosis the probability of developing recurrent thyroid cancer within 10 years never exceeded 45 %. Also, patients who had papillary thyroid cancer recurrence were more likely to die (HR = 1.13, $p < 0.27$) than patients with no recurrence, but not significantly so. Moreover, recurrence in patients with follicular thyroid cancer was protective against all-cause mortality (HR = 0.54; $p = 0.03$). Albeit counterintuitive, this is because recurrence and mortality were competing risks, which was accounted for in the authors' statistical methods.

In addition to the limitations of the SEER data set, SEER-Medicare has the added limitation that nearly all subjects are 65 years of age or over. Thus, this database is generally not useful in diseases that are more commonly diagnosed in younger individuals. Another limitation arises from the SEER policy of tumor staging that is based on a combination of clinical and pathologic examination, however when pathology is unavailable, such as in

nonsurgical treatment of cancer, there is potential bias in the stage comparisons between surgical and nonsurgical cases. In addition, given different modalities for pre-therapeutic assessment of the extent of tumor, patients from different SEER regions who are assigned the same stage category may not be found to be homogeneous with respect to the extent of disease. Medicare claims files are also limited in that they only recently began to include pharmacy claims from Medicare part D. Therefore, only recent patient data includes costs for pharmaceuticals. Lastly, because the SEER-Medicare database contains the numerous medical claims for all cancer patients treated within any of the nine SEER centers, investigators new to research with large datasets may find analyses using SEER-Medicare to be challenging.

Summary

In this chapter we have detailed the specific populations, patient variables, and outcomes available in nine large, publicly available databases that contain endocrine surgery procedures. We provide a brief history of each and note strengths and limitations. In citing a small but representative sample of studies performed using each database, we anticipate the future of clinical research from big data will be equally robust with corresponding progress made in the field of endocrine surgery, and beyond.

Perhaps the most recent, large-scale trend in the field of clinical research, bolstered by the widespread implementation of EHRs, has been the creation and growth of large databases capturing an large volumes of patient data. While advances in medicine and surgery in the twentieth century were largely born out of investigation that consumed significant time and financial resources, the era of big data has facilitated progress in medical and surgical research that is time-efficient and cost-effective. Strengthened by the variety of diagnoses, procedures, and outcomes tracked, modern medicine has benefitted from the timely ability to make clinical associations in patient care as a result. Data collected from a multitude of sources, both clinical and financial, is allowing quality metrics to be benchmarked, with significant implications for health care delivery in the US. It cannot be understated, though, that such conclusions from research using large databases must be drawn acknowledging the inherent limitations of such research, of which selection bias, errors in coding and data entry, and uncertainty regarding validity are but a few. Still, the merits of large database research persist, particularly in light of consistently improving patient outcomes.

The quantity and variety of available databases continues to grow, encompassing greater number of patients, diagnoses, and associated data. For questions related to the realm of parathyroid surgery and other endocrine surgeries, widespread access to CESQIP is highly anticipated. Even beyond the field of endocrine surgery, NSQIP is capturing data pertaining to a multitude of surgical procedures. Databases such as Marketscan, UHC, and the NCDB, are enriched with both inpatient and outpatient data, and outpatient pharmaceutical claims. These features make these databases particular useful and increasingly important to the field of endocrine surgery. Where further gaps in knowledge exist, national databases like SEER and state databases like PHC4 in Pennsylvania are providing answers to pressing health services and clinical research questions.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion

There are several sources of large, publicly available data sets that may be used to address outcomes and health services research in endocrine surgery. Each source of data represents a different population, and has different sets of confounders with which to control. Collaborative research teams can maximize the strengths and minimize the limitations of these data sources to make contributions to quality of care for patients who undergo endocrine surgery.

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Parathyroid Disease: Incidence, Diagnosis, and Management Internationally

45

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Introduction

The parathyroid glands regulate calcium metabolism through release of parathyroid hormone (PTH). Because most parathyroid disorders present with abnormalities of serum calcium, they commonly appear in differential diagnoses [1]. Based on that, every patient with a calcium abnormality should be investigated for parathyroid disorders. Moreover, the prevalence of parathyroid diseases is still unclear in some environments, and understanding the diagnosis and treatment of parathyroid disorders is very important for the head and neck surgeon.

Hypoparathyroidism is the group of diseases characterized by hypocalcaemia with inadequate low PTH levels [2]. The main causes of hypoparathyroidism are: (1) direct injury of the parathyroid gland, usually postsurgical (often, after thyroidectomy), post-irradiation (a rare cause), autoimmune (may be associated with other endocrine insufficiencies), metastatic infiltration (case reports), heavy metal deposition (iron deposition in 10 % of persons with talassemia); (2) transient impairment in parathyroid hormone secretion or action, such as hypomagnesemia related to chronic illness, drugs and acidosis, and hypermagnesemia (for example, in tocolytic therapy and magnesium supplementation); (3) resistance to parathyroid hormone action (pseudohypoparathyroidism); (4) genetic disorders of parathyroid

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hormone synthesis (e.g., autosomal mutations in the PTH gene, as well as X-linked mutations, affecting primarily boys) [1, 3].

Hyperparathyroidism is one of the most common endocrine disorders and is due to increased activity of the parathyroid glands. The cause may be hyperactivity of one or more parathyroid glands, causing hypercalcemia, called primary hyperparathyroidism, or related to a different disease that affects calcium homeostasis, most frequently chronic kidney disease, called secondary hyperparathyroidism and, in some cases, tertiary hyperparathyroidism [4].

Epidemiology

Hypoparathyroidism

Hypoparathyroidism prevalence was reported by Underbjerg and colleagues in the first large-scale study to assess the prevalence of the disease worldwide, in Denmark between 1997 and 2012 [3]. The authors identified a total of 180 patients with nonsurgical hypoparathyroidism with a prevalence of 2.3 cases in 100,000 habitants. Compared with controls, mortality was not increased (HR 1.25; 95 % CI: 0.90–1.73), but patients had a significantly increased risk of renal insufficiency (HR 6.01), cardiovascular diseases (HR 1.91), neuropsychiatric complications (HR 2.45), infections (HR 1.94), seizures (HR 10.05), cataract (HR 4.21), and fractures at the upper extremities (HR 1.93). In contrast, patients had significantly reduced risk of malignant diseases (HR 0.44). Other studies estimated this prevalence between 0.7/100,000 in a Japanese study [5] and 5/100,000 in a study from Rochester in the US [6].

Hypoparathyroidism most commonly occurs after inadvertent damage or removal of parathyroid glands during neck surgery; the occurrence of this surgical complication ranges from 0.5 to 6.6 %, with higher rates after reoperations on the neck [7]. Edafe et al. performed a meta-analysis over a 20 years period including 115 observational studies (61 prospective) [8]. The reported incidence of transient hypocalcaemia was 27 % (interquartile range between 19 and 38 %) and the incidence of permanent hypoparathyroidism was 1 % (interquartile range between 0 and 3 %). They also identified that levels of preoperative calcium, perioperative parathyroid hormone, preoperative 25-hydroxyvitamin D, and postoperative magnesium were independent predictors of transient hypocalcaemia. Factors associated with transient hypocalcaemia in this meta-analysis were: inadvertent parathyroid glands excision (OR 1.90), parathyroid gland auto-transplantation (OR 2.03), Graves' disease (OR 1.75), and female sex (OR 2.28). A calcium level lower than 1.88 mmol/L at 24 h after surgery, identification of fewer than two parathyroid glands at surgery, reoperation for bleeding, Graves' disease, and larger thyroid specimens were identified as independent predictors of permanent hypocalcaemia in multivariable analysis.

Primary Hyperparathyroidism

The estimated incidence of primary hyperparathyroidism is approximately 25 cases per 100,000 persons per year in outpatients of Western countries [9], with a prevalence of one to four per 1000 persons [10]. The disease is probably underdiagnosed in most of the newly developed or developing countries, and the prevalence of the disease has been increasing around the world, with regional and national variations. Some publications suggest that about 1 % of the adult female population in North America and 3 % of postmenopausal women in Scandinavian countries have primary hyperparathyroidism [11–13]. Lower rates, however, have been reported in other regions of the world such as New Zealand (1 per 10,000 population per year) [14] and Hong Kong (3.7 per 100,000) [15].

Other studies showed that the prevalence of primary hyperparathyroidism depends on features of the targeted populations, as well as on the choice of the method employed to detect the disease. Using biochemical population screening, some reports found prevalence of 4.3 per 1000 (in Sweden), 3 per 1000 (Norway), 21 per 1000 (Finland, aged 55–75 years), 1 per 1000 (USA),

and 90 per 100,000 (Austria, [16]). According to the number of patients undergoing parathyroid surgery, the prevalence of hyperparathyroidism in South Korea was 1.4 per 100,000 individual per year. Estimating the true incidence is difficult, but overall figures (UK, USA, and Sweden) are consistently between 27 and 30 per 100,000 person-years [8, 9, 17, 18].

Primary hyperparathyroidism occurs in 0.1–0.3 % of the population and is more common among women than men (1 in 500 compared to 1 in 2000) [19]. In another study, authors identified a female-to-male ratio of 2.8:1 of primary hyperparathyroidism in all age groups, with the incidence increasing after the age of 25 year-old in both sexes [20]. The female-to-male ratio does not change during the peri- and postmenopausal years. In addition, elderly men (69–81 years) had an incidence of primary hyperparathyroidism of 0.73 % in Sweden [21]. The prevalence varies between 0.36 and 13.4 % in postmenopausal women [22]. In Indian series, females were more commonly affected (1.7:1). 71.5 % of the cases were less than 40 years of age, whereas patients from developed nations are generally diagnosed in the fifth and sixth decades [23].

Single gland adenoma is the most common cause (75–85 %), but multiglandular disease may occur, either hyperplasia of the 4 glands or double or triple adenomas (two glands in 2–12 % of cases, three glands in <1–2 %, and four or more in <1–15 %). Parathyroid carcinomas are very rare (~1 %) [4].

Ruda et al. performed a meta-analysis on the association of glandular diseases with primary hyperparathyroidism in 20,225 patients [24]. The authors identified that a solitary adenoma was the most frequent surgical pathology and occurred in an estimated 88.90 % of cases, followed by multiple gland hyperplasia with 9.84 % (multiple gland hyperplasia 5.7 % and double adenomas in 4.1 % of cases) and parathyroid carcinoma in 0.74 % of the patients.

The association between primary hyperparathyroidism and thyroid diseases, either benign or malignant, has long been described. Indeed, up to 65 % of patients with primary hyperparathyroidism have associated thyroid abnormality [25]. However, the association of hyperparathyroidism and Graves' disease is extremely rare [26].

A study investigated the preoperative clinical symptoms and associated conditions of patients with primary hyperparathyroidism comparing two populations, one in San Francisco, USA and the other in Bursa, Turkey. The authors identified that more patients in the United States Group (15 %) had preoperatively persistent or recurrent hyperparathyroidism, whereas Turkish patients had higher serum parathyroid hormone levels and an increased incidence of osteoporosis. Moreover, the size of parathyroid adenomas was significantly greater in Turkish patients (25.2 vs. 17.5 mm) [12].

In the discussion of the article, the authors state that more information is needed regarding the etiology of primary hyperparathyroidism and differences among different races. For example, regional differences in the prevalence of vitamin D deficiency also may contribute to the frequency of primary hyperparathyroidism and its clinical manifestations. Another study reported that most cases of hyperparathyroidism in South Africa were symptomatic at presentation (92.9 %), usually associated with radiologic abnormalities (47.6 %) and significant morbidity [27]. These findings are in contrast with reports from developed countries where many asymptomatic cases were evident in the Western world with the introduction of routine calcium screening [17].

Parathyroid cancer is one of the rarest malignancies, with an incidence of approximately four per ten million persons per year [28]. Other series estimated a prevalence of 0.005 % of all cancers [29–32]. It is a rare cause of primary hyperparathyroidism, accounting for less than 1 % of patients with primary hyperparathyroidism [33]. However, there may be a geographic variation in the distribution of this disease, with reported incidence of about 1 % in Europe and the United States and about 5 % in Japan, Italy, and Korea [34–39]. Parathyroid carcinoma occurs with equal frequency in men and women [40].

Sadler et al. studied 1022 cases of parathyroid carcinoma assessing data from National Cancer Data Base that underwent surgery between 1998 and 2011 [41]. The authors identified that the 5-year

overall survival was 81.1 %. The overall cohort was mainly non-Hispanic (96.5 %), white (77.4 %), and insured (94.3 %), with a median age of 57 years. Mean overall survival was lower and relative risk of death greater in older, African-American patients with a secondary malignancy, with more than two comorbidities, in surgical specimen with positive surgical margins or positive lymph nodes. Multivariate analysis demonstrated that positive lymph nodes (HR 6.47; 95 % CI, 1.81–23.11) and older age (HR 2.35; 95 % CI, 1.25–4.43) were associated with lower overall survival.

Multiple endocrine neoplasia type 1 (MEN-1) and type 2 (MEN-2a), which often include parathyroid neoplasia with primary hyperparathyroidism, occur in about two per 100,000 persons per year [42]. MEN1 represents the most common familial cause of primary hyperparathyroidism, accounting for 2–4 % of all cases, and it is characterized by a predisposition to develop endocrine tumors in pituitary, parathyroid, and pancreatic endocrine cells. Primary hyperparathyroidism, usually with multiglandular disease, is the most common endocrine component of MEN1, occurring in more than 90 % of individuals aged between 20 and 25 years [43, 44].

MEN2A is characterized by an increased risk of pheochromocytoma and parathyroid adenoma or hyperplasia. In MEN2a, primary hyperparathyroidism occurs in 20–30 % of cases. It is usually mild and asymptomatic. The average age of onset of primary hyperparathyroidism is 38 years, many years after the diagnosis of MTC [43, 45].

Secondary Hyperparathyroidism

Secondary hyperparathyroidism is a frequently observed complication in patients with chronic renal failure. The prevalence of secondary hyperparathyroidism is around 45 % among chronic kidney disease patients undergoing hemodialysis, and increases across declining estimated glomerular filtration rate levels [46]. Hyperplasia of the four glands with autonomous disease is the must see in these patients.

The high prevalence of chronic kidney disease patients with secondary hyperparathyroidism with indication of surgical treatment has been recognized in several countries [47]. In Japan, 10 % of the patients on hemodialysis for over 10 years and 30 % of those on hemodialysis for over 20 years, need parathyroidectomy. In 1982, the European Dialysis and Transplantation Association Registry reported 5/1000 patients/year incidence of parathyroidectomy during the second or third year on dialysis, but a rate of over 40/1000 patients/year among those on dialysis for more than 10 years [48]. The *Dialysis Outcomes and Practice Pattern Study* (DOPPS), which assessed the hemodialysis status and quality from 1996 to 2001 in European countries, the United States, and Japan, revealed that surgical treatment is less frequent in Japan than in Europe (4.1 % prevalence, with a 0.6/100 patients/year parathyroidectomy incidence) [49].

A recent published meta-analysis [50] identified that across Europe and Australia, the prevalence of secondary hyperparathyroidism within dialysis populations ranged from 30 to 49 %; prevalence within dialysis populations in the North America (US, Canada) was estimated at 54 %. Within Asia, prevalence estimates were only identified for India (28 %) and Japan (11.5 %). The results of this study are summarized in Table 45.1.

A Brazilian study [47] evaluated the status of secondary parathyroid patients and their need of parathyroidectomy. The prevalence of the disease was 10.7 % when PTH levels were higher than 1000 pg/mL (the cut-off value was one of the limitations of the study). The authors wrote that in Brazil, 68 services perform parathyroidectomy, of which 36 (53 %) are in the south-eastern region. If we consider that Brazil has approximately 92,000 patients on dialysis, and that the estimated prevalence of secondary hyperparathyroidism with indication of parathyroidectomy is 10.7 %, about 9800 patients should be operated on. Three hundred and fifty to five hundred parathyroidectomies are estimated to be performed every year in Brazil, which allows a projection of 20 years before all present surgical indications are met. It is well known that, unfortunately, the

Table 45.1 Prevalence of secondary hyperparathyroidism in dialytic chronic kidney disease worldwide (meta-analysis, [50])

Country	Reference	Population	Year of survey	Ages surveyed (yrs)	SHPT definition	Prevalence (%)
Europe						
Denmark	Dansk Nefrologisk Seiskabs Landsregister (DNSL) [58]	Prevalent renal replacement therapy patients	2010	All	PTH>300 pg/mL	HD=34 PD=32 TX=9
France	DOPPS, Wave 4 [34]	Randomly selected cross section of prevalent dialysis patients; weighted to represent nation	2010	≥18	PTH>300 pg/mL	43.8
Greece	–	–	–	–	–	–
Germany	DOPPS, Wave 4 [34]	Randomly selected cross section of prevalent dialysis patients; weighted to represent nation	2010	≥18	PTH>300 pg/mL	32.1
Italy	DOPPS, Wave 4 [34]	Randomly selected cross section of prevalent dialysis patients; weighted to represent nation	2010	≥18	PTH>300 pg/mL	29.7
Portugal	–	–	–	–	–	–
Russian Federation	Russian Registry of Renal Replacement Therapy[a]	Prevalent hemodialysis patients	2009	All	PTH>300 pg/mL	46.8
Spain	DOPPS, Wave 4 [34]	Randomly selected cross section of prevalent dialysis patients; weighted to represent nation	2010	≥18	PTH>300 pg/mL	32.9
The Netherlands	–	–	–	–	–	–
United Kingdom	DOPPS, Wave 4 [34]	Randomly selected cross section of prevalent dialysis patients; weighted to represent nation	2010	≥18	PTH>300 pg/mL	42.9
Asia						
China	–	–	–	–	–	–
Hong Kong	–	–	–	–	–	–
India	Jeloka et al. [32]	Prevalent dialysis patients	NR	“Adult”	IPTH>300 pg/mL	27.9
Japan	Japanese Society of Dialysis and Transplantation [20]	Prevalent dialysis patients	2012	All	IPTH ≥ 300 pg/mL	11.5
Republic of Korea	–	–	–	–	–	–
Turkey	–	–	–	–	–	–
Oceania						
Australia-New Zealand	DOPPS, Wave 4 [34]	Randomly selected cross section of prevalent dialysis patients; weighted to represent nation	2010	≥18	PTH>300 pg/mL	49.1

(continued)

Table 45.1 (continued)

Country	Reference	Population	Year of survey	Ages surveyed (yrs)	SHPT definition	Prevalence (%)
Americas						
Brazil	Oliveira et al. [59]	Dialysis facilities across Brazil responding to a questionnaire (34 % response rate representing approximately 35 % of the dialysis population)	2010-2011	All	PTH>1000 pg/mL	10.7
Canada	DOPPS, Wave 4 [34]	Randomly selected cross section of prevalent dialysis patients; weighted to represent nation	2010	≥18	PTH>300 pg/mL	54.2
Mexico	–	–	–	–	–	–
United States	DOPPS, Wave 5 [34]	Randomly selected cross section of prevalent dialysis patients; weighted to represent nation	2012	≥18	PTH>300 pg/mL	54

–: Data not available
DOPPS dialysis outcomes and practice patterns study, *HD* hemodialysis; *PD* peritoneal dialysis, *PTH* parathyroid hormone, *TX* renal transplant
[a]By personal communication

access for surgical treatment is also not easy in other developing countries.

Another important cause of hyperparathyroidism is hypovitaminosis D. Recent studies suggest that the prevalence of subclinical vitamin D deficiency is continuously increasing worldwide [51]. The prevalence of vitamin D deficiency depends on the cut-off point used, as well as the type of population studied [52] Therefore, vitamin D deficiency was found in almost all geriatric patients [53], and in 57 % of the American acute symptomatic patients [54]. The prevalence of vitamin D deficiency was 36 % of men and 47 % of women in the European elderly population. Surprisingly, the most southern countries showed the lowest levels [55], and, in women with postmenopausal osteoporosis, the deficiency prevalence ranged from 0 % in Singapore to 3.5 % in the US, and slightly above 10 % in France and Spain [56].

Gomés-Alonso et al. conducted a study evaluating vitamin D levels and secondary hyperparathyroidism in Spain [52]. The authors found that serum 25-hydroxyvitamin D levels were "deficient" (<10 ng/mL) in 27 % of subjects, "borderline" (10–18 ng/mL) in 40 % of subjects, and "normal" (>18 ng/mL) in 33 % of subjects. The prevalence of secondary hyperparathyroidism (PTH>65 pg/mL) according to 25-hydroxyvitamin D levels was 33 % (<10 ng/mL), 16 % (10–18 ng/mL), and 12 % (>18 ng/mL), respectively. There were no cases of secondary hyperparathyroidism with 25-hydroxyvitamin D levels >40 ng/mL. The independent predictors for PTH were 25-hydroxyvitamin D and serum creatinine in both sexes, but age was a predictor only in men. The prevalence of secondary hyperparathyroidism was similar to that found in another study [57] and increased with age, most likely due to the deterioration of renal function and the decrease of 25-hydroxyvitamin D levels. The relationship found between 25-hydroxyvitamin D and PTH was similar to that found in other studies [56] with normal renal function or chronic hemodialysis [58].

A study compared levels of Vitamin D and its association with secondary hypoparathyroidism in two populations: Pakistani and Norwegian [59]. The authors found that measured 25-hydroxyvitamin D was significantly low in the Pakistanis (25.0 vs. 74.8 nmol/L). In addition, the prevalence of secondary hyperparathyroidism (PTH > or =8.5 pmol/L, 25-hydroxyvitamin D <50 nmol/L and Ca^{2+} < or =1.35 mmol/L) was four times higher in Pakistani compared to Norwegian women. Also in Pakistani men, serious vitamin D deficiency defined as secondary hyperparathyroidism was prevalent, and five times as frequent as in Norwegian men.

A Brazilian study evaluated Vitamin D deficiency and insufficiency in elderly people [60]. The authors observed that 40.7 % of institutionalized patients had Vitamin D deficiency and 30.5 % insufficiency. In the outpatient group, the rates were, respectively, 15.8 and 40.0 %. Secondary hyperparathyroidism was identified in 61.7 % of cases in the institutionalized group and in 54 % of cases in the outpatient group.

Diagnosis

Primary Hyperparathyroidism

Seventy to eighty % of patients with primary hyperparathyroidism have no obvious symptoms or signs of disease, with their disease detected by an incidental finding of hypercalcemia [4]. Biochemical assay demonstrate hypercalcemia with parathyroid hormone modestly increased. A flowchart for hypercalcemia evaluation and primary hyperparathyroidism diagnosis was proposed by Fraser [4] and is described in Fig. 45.1.

Once the primary hyperparathyroidism is diagnosed, it is necessary to identify the glandular disease with preoperative localization studies.

In a meta-analysis, Ruda et al. [24] analyzed the sensitivity of preoperative TC^{99m}-sestamibi and high-resolution ultrasound for glandular disease localization in primary hyperparathyroidism as presented in Table 45.2. For solitary adenomas, Tc^{99m}-sestamibi was 88.44 % sensitive. This was higher than the sensitivity of ultrasound, which was 78.55 % for solitary

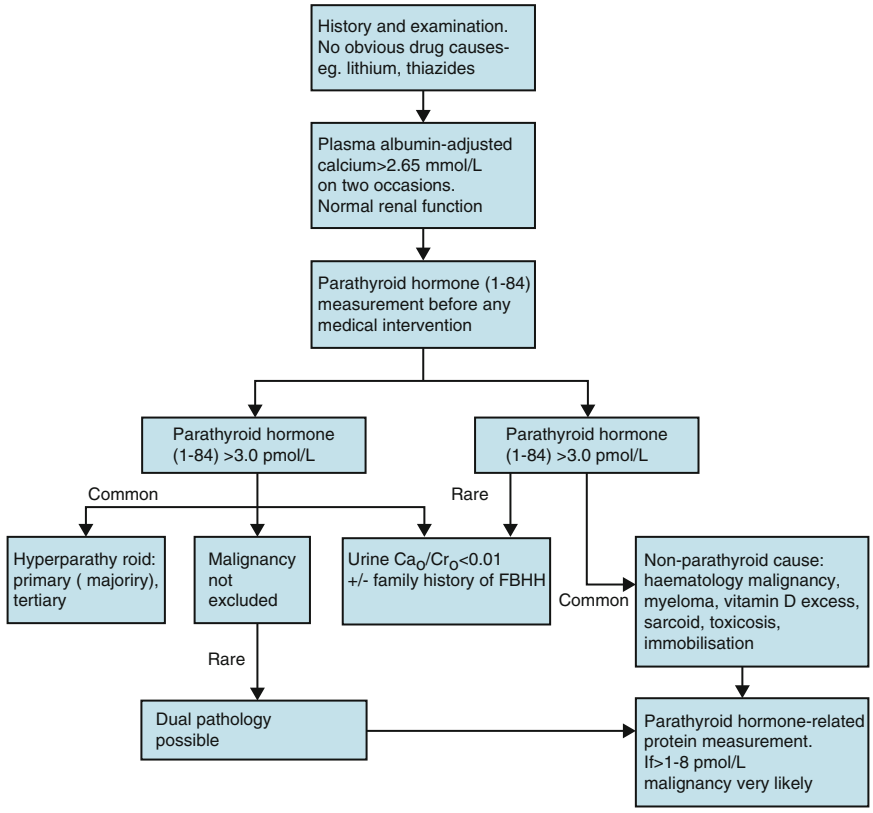

Fig. 45.1 Initial investigation of hypercalcemia. *CaCl/CrCl* calcium creatinine clearance ratio. *FHH* familial hypocalciuric hypercalcemia

Table 45.2 Sensitivity of Tc^{99m}-sestamibi and high-resolution ultrasonography for the histopathologies associated with hyperparathyroidism (meta-analysis, [24])

Diagnostic modalities	Sensitivity (%)	95 % CI
Tc^{99m}-Sestamibi		
Solitary adenomas	88.44	87.48–89.40
Multiple gland hyperplasia disease (glands)	44.46	41.13–47.80
Double adenomas	29.95	−2.19–62.09
Carcinomas	33	33
High-resolution ultrasound		
Solitary adenomas	78.55	77.15–79.96
Multiple gland hyperplasia disease (glands)	34.86	29.86–39.86
Double adenomas	16.20	4.16–28.25
Carcinomas	100	100

adenomas. Preoperative scanning with Tc^{99m}-sestamibi and ultrasound were less reliable for the detection of multiglandular disease. Among all reported cases of hyperplastic gland disease and double adenoma, the sensitivity of sestamibi ranged from 0 to 100 % with an overall mean sensitivity of 44.46 % for multiglandular hyperplasic disease and 29.95 % for double adenoma. Similarly, high-resolution ultrasonography had an overall sensitivity of 34.86 % for multiglandular hyperplasic disease and 16.20 % for double adenoma. Up to 89 % of single parathyroid adenomas can be localized by this method [61].

Other localization studies are: CT scan, MRI, PET-CT, and venography with selective PTH evaluation.

If there is a suspicion of parathyroid carcinoma, especially in patients with PTH >1000 pg/mL and with palpable disease, a comprehensive systemic staging work-up must be performed to look for nodal disease and distant metastasis.

Secondary Hyperparathyroidism

Secondary hyperparathyroidism should be investigated in all people with low 25-hydroxyvitamin D and in all patients with chronic kidney disease. The diagnosis is made by obtaining a pertinent clinical history and examination, plus recognition of the combination of plasma albumin-adjusted calcium, phosphate, parathyroid hormone, 25-hydroxyvitamin D2 or D3, and total alkaline phosphatase in each disease. A localization study is necessary to evaluate the glandular disease in these cases.

Treatment

Primary Hyperparathyroidism

The only cure for primary hyperparathyroidism is surgical removal of a parathyroid adenoma or hyperplasia.

A consensus development panel produced guidelines in 1990, which were updated in 2002 and are again under review, giving specific indications for when surgery is recommended. The National Institutes of Health recommends surgery in the following cases: serum albumin-adjusted calcium greater than 0,25 mmol/L above the upper limit of local laboratory reference range, urine calcium greater than 10 mmol per 24 h, creatinine clearance reduced by 30 % or more, bone mineral density T score less than –2.5 (at any site), age younger than 50 years and under patient request or adequate follow-up unlikely [4].

Experienced surgeons are estimated to identify an affected gland in 95 % of cases. The standard operation is a full neck exploration with identification of all glands, recognizing that 15–25 % can have multiple adenomas, but other minimal approaches are described [4].

Ruda et al. published a meta-analysis, critically analyzing the surgical treatment and the probability of achieving curative normocalcemia [24]. The results are shown in Table 45.3 and demonstrate the similarity of the surgical approaches.

Table 45.3 Probability of cure among surgical procedures for treatment of primary hyperparathyroidism

Surgical treatment	Probability of cure (%)	95 % CI
Minimally invasive radio-guided parathyroidectomy	96.66	95.37–97.94
Unilateral neck exploration	95.25	94.47–96.04
Bilateral neck exploration	97.69	97.36–98.02
Bilateral neck exploration conversion	99.08	97.42–100

Adapted from Ruda et al. [24]

Parathyroid hormone assays with short incubation times have established intraoperative quick assays of this hormone as a method to determine successful removal of an adenoma, assuring that all pathological gland tissue is removed, which can affect intraoperative decisions when localization techniques are equivocal [62–64]. A 50 % decrease in parathyroid hormone from baseline 5–10 min after excision of an adenoma strongly suggests a successful parathyroidectomy. Delaying the harvest of the blood sample to be analyzed at least 30 min after excision can improve sensitivity. The debate about the value of intraoperative parathyroid hormone and the role of minimally invasive parathyroidectomy continues, with some authors supporting this technique [65] while others state that a bilateral approach still offers the best opportunity for long-term cure [4, 66].

In the meta-analysis of Ruda et al. [24], intraoperative PTH measurement gave true-positive test results in 98.4 % of cases in which it was used. Intraoperative PTH gave false-positive results in 3.37 % of cases when declines of greater than 50 % were judged as indicative of cure and the patient was not rendered normocalcemic. Results of intraoperative PTH were considered to be false negative in 1.94 % of cases when a less than 50 % decrease was observed, indicating fallaciously the presence of unresected diseased parathyroid glands in the neck.

Complete surgical resection with microscopically negative margins is the recommended treatment for parathyroid cancer and offers the best

chance of cure. Successful resection is dependent on preoperative suspicion and intraoperative recognition. Upon intraoperative recognition of malignant features as described above, the surgeon should perform en bloc resection of any involved tissues with no rupture of the tumor capsule. Hence, the threshold to include the adjacent thyroid lobe as well as level VI/VII lymph nodes must be very low. In fact, the en bloc resection of the suspicious parathyroid gland with the adjacent thyroid lobe and adjacent levels VI/VII lymph nodes has been recommended, but with no objective evidence that it improved survival [40].

Secondary Hyperparathyroidism

The treatment of hyperparathyroidism due to low 25-hydroxyvitamin D levels is supplementation of calcium and vitamin D. This therapy has a beneficial effect on fracture incidence. However, for most active elderly people, higher doses of calcium and vitamin D may be required to reduce fracture incidence [4].

The parathyroidectomy is indicated in the treatment of refractory hyperparathyroidism secondary to chronic kidney disease. The parathyroidectomy is an effective and safe procedure that can significantly reduce PTH and phosphate levels [67].

The Brazilian Society of Nephrology indicates the parathyroidectomy for hyperparathyroidism secondary to chronic kidney disease in the following situations: PTH levels persistently over 800 pg/mL with refractory hypercalcemia and/or hyperphosphatemia, presence of parathyroid glands larger than 1 cm^3 at ultrasound, patients with extraosseus calcifications or uremic calcific arteriolopathy, and refractory progressive and debilitating advanced osseous disease. The surgery is also indicated in the persistence of hyperparathyroidism after 1 year of a functional kidney transplant associated with persistent hypercalcemia (tertiary hyperparathyroidism) [67].

The parathyroidectomy in this situation must include the exploration of all glands. There are basically three surgical options in these cases: total parathyroidectomy, subtotal parathyroidectomy, and total parathyroidectomy with heterotopic autotransplantation. In a recent meta-analysis comparing these three techniques, the authors could not establish a consensus about the procedure of choice. The authors identified that total parathyroidectomy with heterotopic autotransplantation was the procedure of choice in 32.65 % of the studies and concluded that the decision depends on surgeon experience and skill [67]. The recurrence rate varied between 0 and 4 % for total parathyroidectomy, while it was 7 % for total or subtotal parathyroidectomy with heterotopic autotransplantation.

Summary

Hyperparathyroidism does not have equal prevalence around the globe. Increases incidence in the western world may be the result of more prevalent biochemical testing of those populations. Differing practice patterns from many unique health systems result in distinct regimes for biochemical testing and imaging. Surgery is the universal treatment for primary hyperparathyroidism although surgical approaches differ based on surgical traditions, patient access, and available technologies.

Society Guidelines: N/A

Best Practice: N/A

Expert Opinion
International best practices for treating hyperparathyroidism vary based on local conditions and resources but are largely grounded in the principles of western medical practice.

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Complications of Parathyroid Surgery

46

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Contents

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Introduction

Given the anatomical, functional, and vascular characteristics of the parathyroid glands, surgical intervention of these structures has an inherent risk that, while seldom life-threatening, can have devastating and life-long consequents for the patient. It is important to highlight that most of the complications associated with parathyroidectomy are avoidable with a thorough understanding of the anatomy, appropriate patient selection, and meticulous surgical technique. The risk profile of parathyroid surgery varies significantly depending on the disease status, previous interventions, and patient comorbidities; an experienced surgeon should be able to take all of these variables into account, and convey a proper estimation of the individualized risk assessment to the patient.

The reported procedure-specific, long-term morbidity rate associated with primary parathyroidectomy is only 1 % [1]. However, the risk of complications increases exponentially in the context of reoperative surgery, where it has been reported as 27–54 % [2–5], while in the geriatric population where it ranges from 4 to 10 % [6].

Mortality from elective parathyroid surgery is extremely rare, approaching 0 % in the vast majority of contemporary reports [1]. It is, however, considerably higher in the geriatric population, where it consistently approaches 1 % [7–9],

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and has been reported to be as high as 10 % [6]. The elevated mortality rate in this subset of patients appears to be related to presence of medical comorbidities, and not to a higher rate of surgical complications [6–9].

Below we describe the most common complications of parathyroid surgery and discuss their etiology, management, and most importantly, the technical considerations necessary to avoid them.

Postoperative Hypocalcemia

Hypocalcemia is one of the most common complications after parathyroid surgery. Depending on its temporal progression, postoperative hypocalcemia can be defined as transient or permanent, depending on if it extends beyond 12 months postoperatively [10]. While hypocalcemia and hypoparathyroidism are used indistinctly in the literature they are not necessarily the same, and it is possible to have hypocalcemia with normal PTH levels, and symptoms of hypocalcemia in eucalcemic patients [10]. The incidence of transient postoperative hypocalcemia among patients treated for primary hyperparathyroidism is 15–30 % [1], but recent series report lower incidences. Miccoli et al. report a 2.7 % incidence in patients treated with video-assisted parathyroidectomy [11], while in a series of 656 patients Udelsman reports an incidence of only 0.5 % [12]. A randomized trial comparing bilateral neck exploration vs. minimally invasive parathyroid surgery (MIPS) showed that while transient postoperative hypocalcemia was more frequent with open exploration, there were no differences in symptomatic or permanent hypocalcemia [13].

Overall, at 0.1 % the risk of permanent hypocalcemia is extremely low for patients undergoing primary parathyroid surgery; [14] however, it rises exponentially in the context of reoperative parathyroidectomy where is as high as 15–30 % [10]. The individual risk for postoperative hypocalcemia is in direct correlation with the activity of the parathyroid adenoma and its functional impact. Patients with preoperative bone pain, elevated alkaline phosphatases and serum PTH greater than 500 pg/ml have a significantly higher risk of postoperative hypocalcemia and in extreme cases, even risk of hungry bone syndrome. Transient hypocalcemia is routinely managed with calcium supplementation in an outpatient basis, while permanent hypocalcemia requires close follow up, appropriate counseling and specialized management.

Two main etiopathogenic mechanisms are behind the development of postoperative hypocalcemia. First, the presence of a parathyroid adenoma functionally suppresses normal parathyroid glands. This suppression, in combination with the short half-life of PTH (3–5 min), can precipitate transient hypocalcemia after surgical ablation of the adenomatous gland, especially in patients preoperative PTH well above the normal range. In this setting, hypocalcemia is unavoidable, as it truly represents a homeostatic adjustment secondary to abrupt changes in serum PTH levels. The second mechanism is surgical manipulation of the parathyroid glands. In this setting, trauma to the gland's delicate vascular pedicle results in vasospasm and transient ischemia, which clinically presents as a temporary functional impairment also known as "parathyroid stunning." The degree and extension of the parathyroid dysfunction is proportional to the level of trauma; complete devascularization of the glands will invariably lead to permanent loss of function and depending on the number of glands affected, potentially to permanent hypoparathyroidism.

Since surgical trauma is preventable, the importance of thorough knowledge of the vascular anatomy, meticulous dissection, and bloodless surgical field cannot be overemphasized. From the vascular standpoint, in most cases the blood supply to the superior and inferior parathyroid gland comes from the inferior thyroid artery [15], although the superior gland may occasionally receive vascularization from the superior thyroid vessels (Fig. 46.1). In order to preserve the vascular integrity of the parathyroids, the same surgical principles used for a thyroid surgery should be applied: maintaining the dissection plane at the level of the thyroid capsule, ligating branches of the inferior thyroid artery as distally as possible, and performing a controlled ligation of the superior thyroid vessels, after ruling out the presence of direct contributions to the superior parathyroid gland [15, 16].

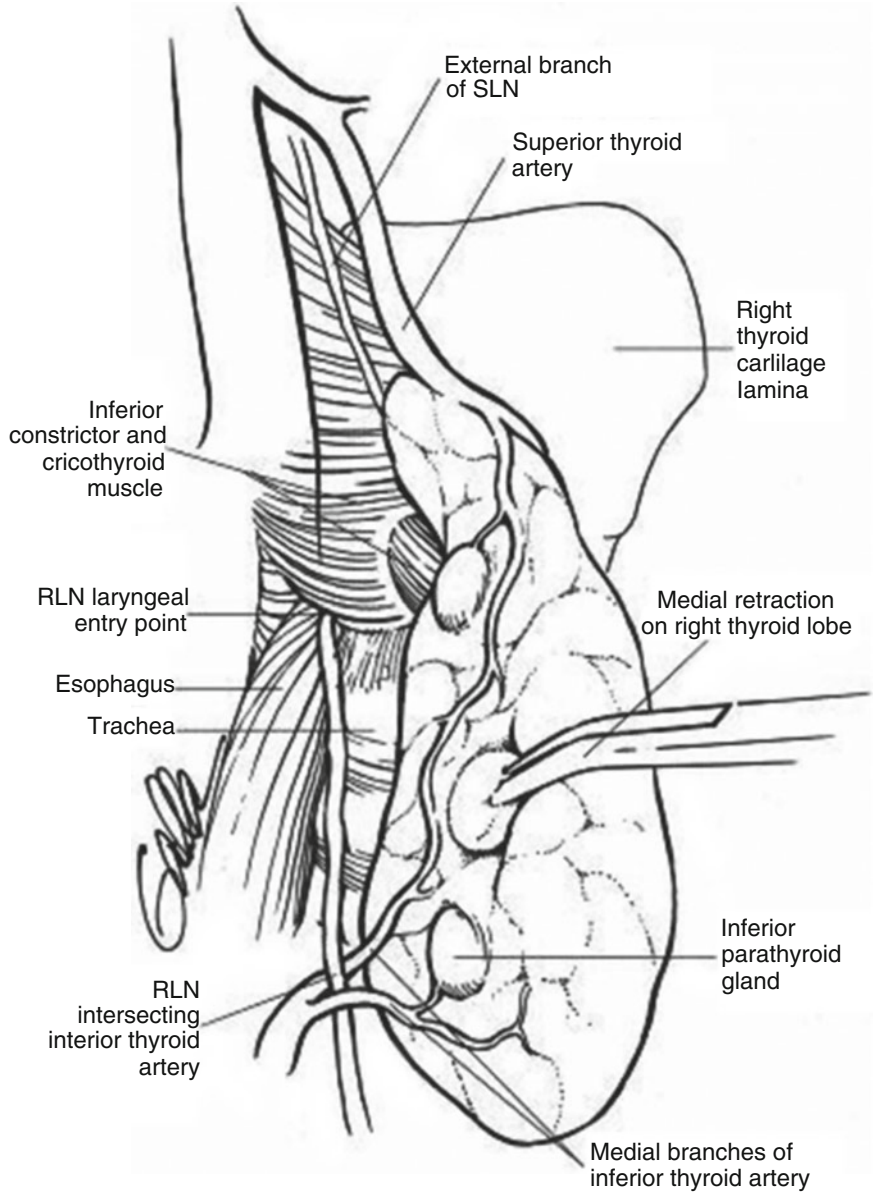

Fig. 46.1 Vascular supply of the parathyroid glands and relationship with the thyroid gland and recurrent laryngeal nerve. Surgery of the Thyroid and Parathyroid Glands Edition 2, Greg W. Randolph, editor, Elsevier Saunders Philadelphia 2012

Recurrent Laryngeal Nerve Injury

The risk injury to the recurrent laryngeal nerve (RLN) is inherent to any surgical procedure involving the central compartment of the neck. For surgeons, the best strategy to prevent nerve injury is to be familiar with the normal anatomy—including its variations—and most importantly, the anatomical relationships of the RLN and parathyroid glands.

Both the right and left RLN originate as braches of the vagus nerve in the thorax. In the right side the recurrent nerve emerges posteriorly

as the vagus crosses the subclavian artery, while in the left side it does so as the vagus crosses over the aortic arch. After circumventing subclavian artery and aortic arch and respectively, both nerves ascend along the tracheoesophageal groove towards the laryngeal inlet. In contrast with the near-vertical path of the left RLN, the right nerve has a more oblique course, explained by its relatively lateral point of inflection. As the RLN ascends in the neck, it becomes intimately related to the thyroid gland and to the inferior thyroid artery (ITA). In roughly 65–70 % of the cases the nerve courses deep to ITA, in 20–25 % of the cases is superficial to the vessel, and it courses between the ITA branches in approximately 5 % of the cases [17], as shown in Fig. 46.2. In light of variable relationship between the RLN and the ITA, we recommend against using this vessel as the sole anatomical landmark for the identification of the nerve. Also, an anatomical study suggests that the ITA is absent in 6 % of the population [18], further underscoring this concept.

During its cervical course, the RLN branches prior to its point of entry into the larynx in 20–65 % of the cases [19–21], commonly in an anterior and a posterior branch. In this setting, most authors agree that anterior branch contains the majority of the motor fibers—both abductor and adductor—while the posterior branch is predominantly sensory [22]. The surgeon must be able to promptly identify the presence of RLN branching during the course of the dissection, as this anatomical variation has been associated with a twofold increase in the risk of RLN injury [23].

Intraoperative electrophysiologic recurrent laryngeal nerve monitoring (EMG) can be a useful tool in the identification of the RLN, particularly in challenging situations such as reoperative parathyroidectomy. While nerve monitoring has not proven to decrease the incidence of RLN injury, it has a well-documented prognostic role. In a recent study involving almost 1000 at-risk nerves, Genther et al. report a sensitivity of 95.5 % and a specificity of 99.2 % of EMG for identification of immediate postoperative vocal cord paralysis in patients undergoing thyroid- or parathyroidectomy [24].

Is important for the surgeon to clearly assess and document the patient's vocal status pre- and postoperatively, as patients with a well-compensated vocal cord paresis or paralysis can present with a normal voice. The author's preference is to visualize the larynx through an indirect laryngoscopy preoperatively in all patients as this is a noninvasive procedure that allows for documentation of the vocal cord function, and serves as a reference for future examinations. If the patient presents with any vocal impairment and/or the vocal cords can't be properly visualized with this technique, a flexible fiberoptic laryngoscopy should be considered [22]. The same approach is recommended postoperatively, where functional

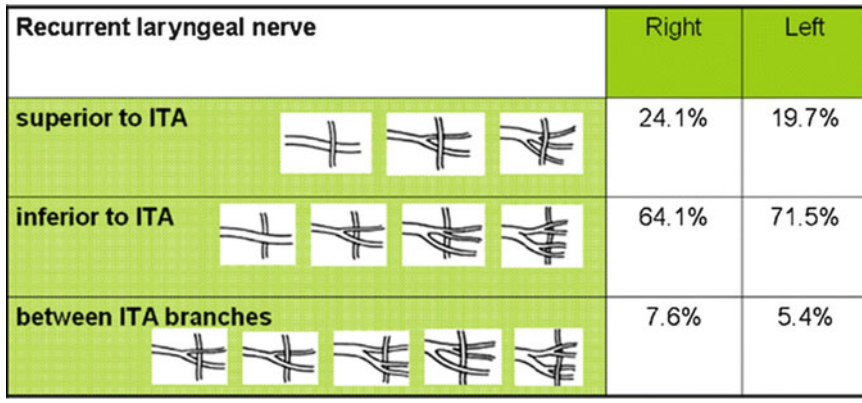

Fig. 46.2 Distribution of the anatomical relationship between the recurrent laryngeal nerve and the inferior thyroid artery Makay et al. [17]

manifestations of an acute RLN injury are not always obvious and may take some time to develop. Immediately after denervation, the balance of adductor and abductor musculature causes the vocal cord to migrate to a paramedian position. In this location the contralateral vocal cord may often compensate for the deficit, resulting mild symptomatology. In this context, patients often complain of a "weak" or raspy voice which not uncommonly is attributed to endotracheal intubation [25]. As the cord lateralizes—over the period of days to weeks—progressive hoarseness and vocal fatigue ensue, and patients develop a characteristic "breathy" voice that reflects the presence of an uncompensated glottic gap.

Postoperatively, surgeons should maintain a high index of suspicion for RLN injury. Should a patient present with a vocal cord paralysis, he or she should be counseled and promptly referred for specialized care. The chances for spontaneous recovery of the nerve function greatly depend on the mechanism and severity of the injury. Neurapraxia usually results from traction- or thermal injury to the nerve, and it has a better chance of spontaneous recovery than those cases where the nerve was transected. The treatment of unilateral vocal cord paralysis includes operative and nonoperative management and depends on the functional impact, patient's vocal needs, and estimated changes for spontaneous recovery. Vocal cord medialization or thyroplasty are commonly performed in patients in whom recovery not anticipated based on the temporal profile and/or electromyographic findings.

Bilateral vocal cord paralysis is an extremely rare occurrence in the context of parathyroidectomy, but still worth noting given its life-threatening implications. In this scenario, both vocal cords migrate to paramedian position causing an acute airway obstruction that clinically presents as stridor. This usually becomes obvious as soon as the patient is extubated, but may go unrecognized until the patient is in the recovery room. Bilateral vocal cord paralysis is a medical emergency, and the goal in this setting is to promptly secure the airway. This is most commonly achieved through endotracheal intubation, but the surgical team should ready to establish a surgical airway.

Is important to recognize that in 0.3–4% of the cases the nerve has no nonrecurrent course and originates directly as a cervical branch of the vagus nerve, without entering the mediastinum [26] (Fig. 46.3). This anatomical variation is explained by an embryological involution of the fourth aortic

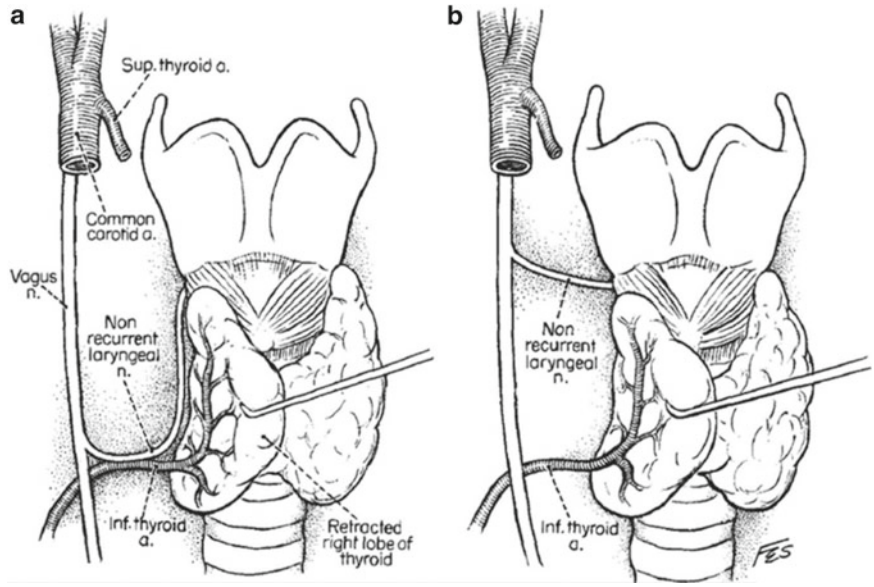

Fig. 46.3 Variations of nonrecurrent recurrent laryngeal nerve. Surgery of the Thyroid and Parathyroid Glands Edition 2, Greg W. Randolph, editor, Elsevier Saunders Philadelphia 2012

arch which causes the subclavian artery to arise from directly from the aortic arch [27]. In these cases the right subclavian artery commonly has a retropharyngeal course (*arteria lusoria*) where it can cause organic esophageal obstruction that presents as dysphagia lusoria [28]. Left-sided nonrecurrent laryngeal nerves are extremely rare. They occur only in the context of situs inversus and patients present with a corresponding left retropharyngeal subclavian artery [28].

Overall, the risk of recurrent laryngeal nerve injury after parathyroidectomy has been reported to be below 1 % in most series regardless of the type of surgical approach [6, 11, 12, 14, 29, 30]. Few studies have directly compared the risk of RLN injury between surgical techniques. In a series of 1300 patients treated at a teaching hospital for benign primary hyperparathyroidism, Karakas et al. [31] reported an incidence of permanent vocal cord paralysis of 0.4 % for minimally invasive parathyroidectomies vs. 2 % for bilateral open exploration. However, other series have found comparable rates of RLN injury between neck exploration (0.7 %) and MIP (0.8 %) [12], suggesting that the surgeon's experience might play a more significant role than the surgical approach utilized.

In a reoperative setting the presence of scar tissue, loss of anatomical landmarks and frequent need for more extensive dissection inherently increase the risk of RLN injury. A recent study describes a 9 % permanent vocal cord paralysis in patients undergoing revision surgery for persistent or recurrent hyperparathyroidism [3], almost a tenfold increase over the reported rate for primary surgery. Preoperative counseling, baseline laryngeal examination, and intraoperative EMG laryngeal monitoring should be considered in all patients undergoing a revision parathyroidectomy.

Persistent and Recurrent Hyperparathyroidism

Biochemical cure is defined as eucalcemia and normalization of serum PTH at 6 months postoperatively. Persistent hyperparathyroidism is defined as a PTH elevation within 6 months of surgery, while recurrent hyperparathyroidism is defined as PTH elevation beyond 6 months postoperatively, following a period of normalization. Since most of the surgical failures are preventable, it is worth discussing the process of patient selection and technical aspects of the surgery.

Primary hyperparathyroidism is caused by a single adenoma in 85–95 % of the cases [32–36], and a second adenoma is present in 3–5 % of the patients [37]. The incidence of 4-gland hyperplasia ranges between 2 and 6 %, but has been reported to be as high as 15 % [35, 36]. Parathyroid localization allows the surgeons to differentiate single vs. multigland disease preoperatively. Those patients with localizing disease (80–90 %) are candidates for a unilateral (minimally invasive) parathyroidectomy. The options for preoperative localization include: neck ultrasound, Sestamibi-SPECT, CT scan with and without contrast (4DCT), and magnetic resonance imaging (MRI). These test are not mutually exclusive and can be combined in an attempt to increase the accuracy of localization. Sestamibi-SPECT is by far the most commonly utilized, and currently considered as part of the standard of care. However, 4DCT has been rapidly adopted as it has demonstrated better sensitivity than Sestamibi (88 % vs. 65 %) and better ability to identify multigland disease (85 % vs. 25 %) [38–40].

Bilateral neck exploration without preoperative localization has long been considered the "gold standard" for surgical treatment of primary hyperparathyroidism [37]. The advent of reliable localization studies led to the development of minimally invasive parathyroid surgery and has radically changed the practice patterns over the last decades. Currently, MIP is the preferred approach for primary hyperparathyroidism when a single adenoma can be localized preoperatively, with surgeons increasingly adopting this approach over bilateral exploration [41, 42]. Minimally invasive parathyroidectomy is based on the excision of a single, well-localized parathyroid adenoma and is applicable to 90 % of the patients presenting

with sporadic primary hyperparathyroidism [43]. In addition to the localization studies, intraoperative parathyroid hormone monitoring (IOPTH) plays a role in identifying patients who may need a bilateral exploration. The main purpose of IOPTH is to identify patients with multigland disease—which account for 5–15 % of the patients [13]—during the course of the operation, In the presence of multigland disease, the sensitivity of Sestamibi drops from 97 to 61 % and the specificity from 93 to 84 % [44]. The "Miami" criteria are defined as IOPTH drop of ≥50 % from baseline at 10–15 min post-excision [45], with most experts agreeing that the post-excision IOPTH should be also be within normal limits [46]. If these criteria are not met after the resection of the suspected adenoma, further exploration is warranted. Multiple series have documented a slight increase in biochemical cure rate with the use of IOPTH from 95–97.5 to 97–99 % [12, 43, 47–50], although this difference has failed to reach statistical significance in any of the series.

At this stage, the decision of bilateral neck exploration vs. MIPS greatly depends on the surgeon's preference and expertise, although recent evidence seems to support minimally invasive approaches. Randomized trials comparing both techniques—presented in Table 46.1—consistently show equivalent cure rates even at 5-years postoperatively [51]. In a similar fashion, surgical resection of parathyroid adenomas through an <2 cm incision has been associated with shorter operative time, decreased pain and length of hospital stay, and better cosmetic results [52].

Overall, the success rate of surgery for primary hyperparathyroidism ranges between 94 and 99 % [11, 12, 31, 32, 35, 50, 53]. However, these outcomes must be interpreted cautiously, as most series come from high-volume, expert surgeons in centers with access to high-quality imaging and perioperative support [37], and may not accurately reflect surgical outcomes in less experienced hands. Worldwide, most parathyroid surgery is not performed by high-volume surgeons. This is also the case in the United States, where 78 % of the parathyroidectomies are performed by surgeons for whom endocrine case volume accounts for less than 25 % of their practice [54]. Several studies have suggested that surgeon's expertise and case volume is associated with better outcomes. In a study including 159 revision parathyroidectomies, Chen et al. [55] compared the surgical volume of the centers performing the initial failed operations and concluded that patients who underwent their initial procedure at low-volume centers (<50 parathyroidectomies/year) had almost a sevenfold increase in preventable operative failure, defined as missing an adenoma in a normal anatomical location. Similarly, a study based on the Scandinavian national registry comparing outcomes between high- and low-volume centers found biochemical cure rates of 90 % for endocrine surgery centers, 76 % for general surgery clinics, and only 70 % for centers performing less than 10 cases/year [56].

Invariably, the reasons for surgical failure include missing a single adenoma and failure to identify multigland disease. While preoperative localization studies collectively represent a major advance in the field, no technique can replace a thorough understanding of the role that embryology plays in the genesis of parathyroid adenomas. Every parathyroid surgeon should be able to perform a bilateral neck exploration and directly "look" for a missing adenoma in the most common locations. The superior parathyroid glands arise from the fourth branchial arch and have a relatively constant location, in the posterior aspect of the superior thyroid pole, adjacent to the cricothyroid junction and recurrent laryngeal nerve [34]. The inferior parathyroid glands arise from the third branchial arch and descent towards the thymus; while they are routinely located at the level of the inferior thyroid pole, they can be in any location within their embryological path. As such, their location is much more variable. A nomenclature system that uses mnemonic associations provides an easy way for uninitiated parathyroid surgeons to systematically explore common sites where adenomas could be missed [30] (Fig. 46.4).

Table 46.1 Outcomes of randomized trials comparing minimally invasive parathyroidectomy with bilateral neck exploration Callender et al. [37]

Authors	No. of patients	Randomized group (no.)	Results
Slepavicius [83]	48	MIP (24), BNE (24)	No difference in OR time, cosmesis at ≥1 year, or cure rate (100 % in both arms); less pain, better cosmesis at <1 year in MIP group; lower cost in BNE group
Miccoli [84]	40	Video-assisted MIP (20), endoscopic BNE (20)	No difference in OR time, complications (none), cure rate (95 % MIP, 100 % BNE); 3 BNE patients with single adenoma had additional "unnecessary" glands removed
Aarum [85]	100	MIP (50), BNE (50)	No difference in cure rate (96 % MIP, 94 % BNE); cost 21 % higher for MIP group; >50 % of MIP group actually underwent bilateral exploration
Sozio [86]	69	Radio-guided MIP (34), BNE (35)	No difference in cure rate (100 % in both arms); shorter OR time, LOS, and recovery time in MIP group
Bergenfelz [87]	50	MIP (25), BNE (25)	No difference in cure rate (96 % MIP, 100 % BNE); shorter OR time, less short-term hypocalcemia in MIP group
Bergenfelz [13] and Westerdahl & Bergenfelz [51]	91	Initial study: MIP (47), BNE (44); 5-years follow-up: MIP (38), BNE (33)	No difference in cost, temporary nerve palsy (2 MIP, 1 BNE), short-term cure rate (98 % in both arms), long-term cure rate at 5 years (89 % MIP, 94 % BNE); shorter OR time, less short-term hypocalcemia, less early severe symptomatic hypocalcemia, less long-term hypocalcemia in MIP group; 1 BNE patient with single adenoma still dependent on calcium/calcitriol at 5 years
Miccoli [88]	38	Video-assisted MIP (20), BNE (18)	No difference in cure rate (100 % in both arms); shorter OR time, less pain, better cosmesis in MIP group; no complications in BNE group vs. 1 RLN palsy in MIP group

BNE bilateral neck exploration, *LOS* length of stay, *MIP* minimally invasive parathyroidectomy, *OR* operating room, *RLN* recurrent laryngeal nerve

Reoperative parathyroid surgery is challenging and should be reserved for experienced surgeons in high-volume centers. Cure rates following reoperative parathyroidectomy are significantly lower than for primary surgery, ranging from 83 to 96.8 % [5, 57–59], and reoperative parathyroidectomy is associated with a higher complication rate [2–5]. Reoperations are also significantly more expensive, with a cost that roughly doubles that of the initial surgery [60]. As the risk/benefit balance significantly differs from the initial parathyroidectomy, candidates for reoperative surgery should be carefully evaluated. In these cases multiple localization studies are routinely performed looking for concordant findings which suggest an area of "high probability" to identify the adenoma. With localization protocols currently available, blind neck re-explorations should virtually never be required [37]. Anatomically, the missed adenomas will almost invariable be located along the embryological path of descent of the parathyroids. This is demonstrated in Fig. 46.5 which shows the anatomical location of missed adenomas in a series of 130 reoperative parathyroidectomies [61]. Technical advances will continue to impact

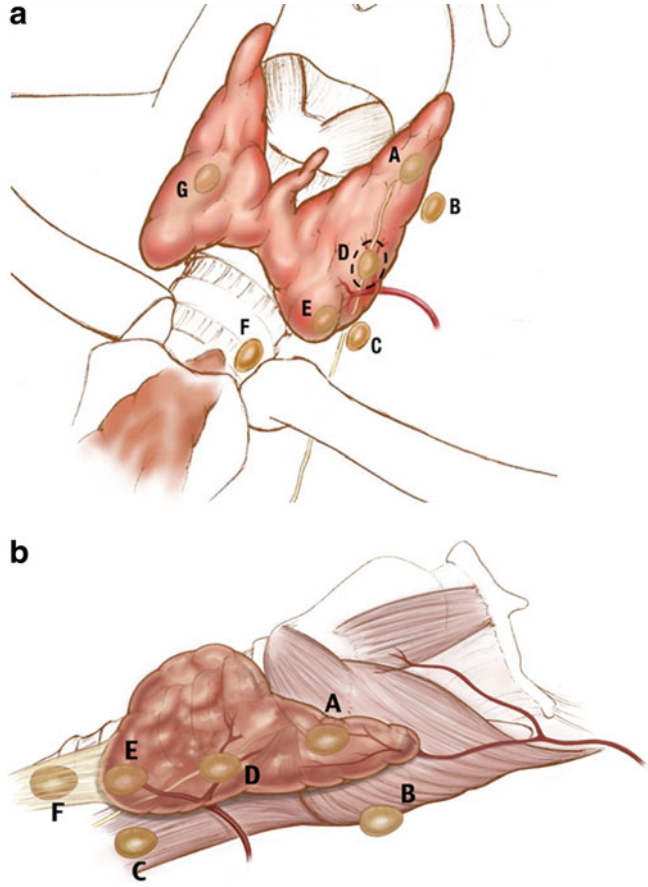

Fig. 46.4 (**a**) The "Perrier" classification; common locations of parathyroid adenomas Moreno et al. [30]. Type A: Adherent to the posterior thyroid parenchyma. A type A gland is in the accepted, expected location of a normal parathyroid gland. Type B: Behind the thyroid parenchyma. A type B gland is exophytic to the thyroid parenchyma and lies in the tracheoesophageal groove. Type C: Caudal to the thyroid parenchyma, in the tracheoesophageal groove. A type C gland is more inferior than a type B gland on lateral images and located inferior to the inferior pole of the thyroid (**c**loser to the **c**lavicle). Type D: Directly over the recurrent laryngeal nerve at the level of the inferior thyroid vessels. The dissection may be difficult because a type D gland is **d**angerously close to the recurrent laryngeal nerve. Type E: Located in the internal aspect of the inferior pole of the thyroid. A type E gland is in a location that is more superficial in an anterior–posterior plane than the recurrent laryngeal nerve. It is the **e**asiest to resect. Type F: "Fallen" into the thyrothymic ligament, below the inferior pole of the thyroid in a pretracheal plane. A type F gland is frequently referred to as an ectopic gland, and its resection usually involves transcervical delivery of the thyrothymic ligament or superior portion of the thymus. Type G: True intrathyroidal gland location. (**b**) Common location of parathyroid adenomas, lateral view

the management these patients. MRI-based, real-time intraoperative localization has been successfully tested in a small cohort of patients [62]. This, and similar techniques, will further add to the surgical armamentarium in the treatment of persistent and recurrent hyperparathyroidism.

Conversion to Bilateral Neck Exploration

In the context of minimally invasive surgery, conversion to bilateral exploration must not be viewed as a complication, but rather as part of

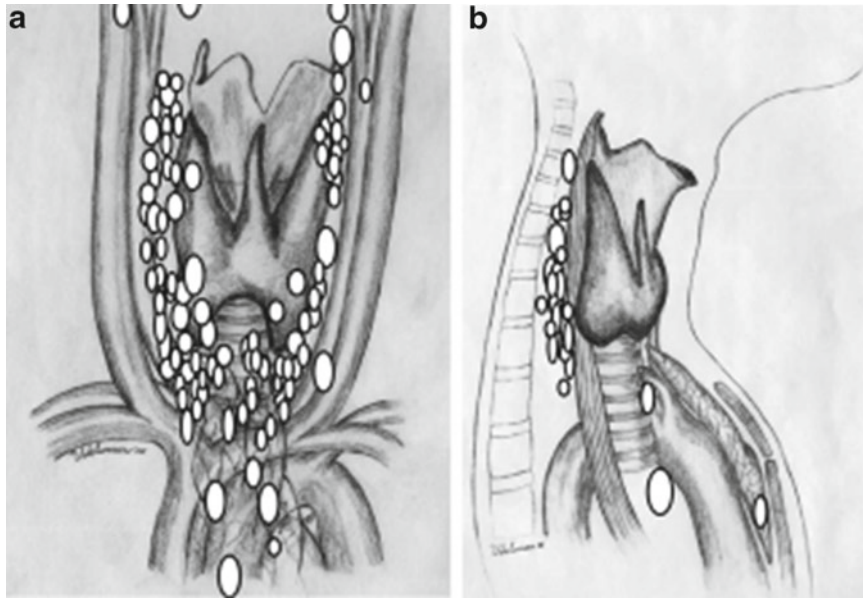

Fig. 46.5 The locations of parathyroid glands identified during reoperative parathyroid surgery are illustrated, including (**a**) an anterior–posterior view and (**b**) a lateral view Udelsman et al. [61]

a surgical continuum in an attempt to achieve biochemical cure. Failing to identify an abnormal parathyroid gland, or an insufficient drop in IOPTH following the resection of the suspected adenoma are probably the most common factors leading to the decision to convert from a minimally invasive approach. Other factors may also lead to the decision to convert to bilateral neck exploration, as reported by Norman et al. in a prospective series of 3000 consecutive patients. In this study, the authors identified the following intraoperative findings leading to open exploration: involvement of the recurrent laryngeal nerve, contralateral thyroid disease discovered, extensive scar tissue, abnormal ipsilateral gland, failure to identify ipsilateral gland and insufficient parathyroid hormone reduction [63]. Overall, there are many situations in which converting to bilateral neck exploration represents the most sensible approach and reflects appropriate surgical judgment. It is important for the surgeon to disclose the limitations of minimally invasive techniques, and to discuss the potential need for bilateral exploration in all cases.

Neck Hematoma

Hematomas of the central compartment are most commonly associated with thyroid surgery, but this complication may present after parathyroidectomy, although with a very low incidence. In a study comparing bilateral cervical exploration vs. MIPS, 0.2 % of the patients presented with hematoma after open approach while 0.8 % had a hematoma after MIPS [12]. Udelsman reports a 0.2 % incidence in a cohort of 1,650 consecutive patients [14] while Miccoli describes a 0.27 % incidence in patients treated with video-assisted parathyroidectomy [11].

In spite of their rarity, tension hematomas of the central neck compartment represent a serious, and potentially life-threatening complication that is worth noting. Acute bleeding in a nondistensible surgical cavity significantly increases the pressure in the larynx and perilaryngeal structures. This leads to venous congestion of the airway, edema of the supraglottic structures, and neurapraxia of the RLN which results in bilateral vocal cord paralysis. Patients present with noisy breathing or laryngeal stridor,

and characteristically adopt the tripod position trying to alleviate the pressure over the airway. A high index of suspicion is necessary as the diagnosis is based on clinical findings and patients can deteriorate rapidly. As early as the diagnosis is suspected, the surgical incision must be reopened to evacuate the hematoma. This maneuver usually alleviate the symptoms and stabilizes patient enough to proceed with a formal neck exploration.

Wound Infection

Overall, the risk of wound infection is extremely low. Parathyroid surgery is considered a clean surgery, so the wound infection rate should not exceed 1 %. A recent study of 776 patients undergoing parathyroidectomy reports a 0.3 % incidence of postoperative wound infection [64]. Like any elective surgery, routine, single-dose antibiotic prophylaxis should be used for all patients.

Adverse Scarring

In general, parathyroidectomy incisions are nearly invisible when fully healed. However, just like in any surgical procedure, there is low risk of adverse scarring that should always be disclosed to the patient. African Americans and patients with history of keloids or exuberant scars should be approached cautiously. A good practice is to ask the patient to reveal previous surgical scars to anticipate potential wound complications. Intraoperatively, the incision should be placed in a skin crease if at all possible. Care must be exercised with skin retraction, particularly in small incisions that provide limited exposure. Excessive retraction traumatizes the skin edges, leaving a short but noticeable scar in the neck. If the exposure is insufficient, is better to extend the incision than to risk an unsightly scar derived from excessive retraction. If a keloid scar is identified postoperatively, compression therapy, and intralesional corticosteroids should be initiated as early as possible.

Methylene Blue Toxicity

Intravenous administration of methylene blue has been used to identify abnormal parathyroid glands in patients with primary hyperparathyroidism. In a recent series of almost 100 patients, intravenous methylene blue appropriately stained close to 80 % of the glands [33]. The use of methylene blue has been associated with serotonin syndrome, a rare form of encephalopathy most frequent in patients under treatment with selective serotonin reuptake inhibitors (SSRIs) drugs [65]. This condition is characterized by autonomic, neurological, and neuromuscular instability presenting in the postoperative period. Clinical suspicion is important to recognize this condition. The treatment usually involves support measures as most cases resolve spontaneously within days. Since depressive symptoms are common in patients with primary hyperparathyroidism, use of SSRI should be directly inquired and the use of methylene blue should be avoided in these patients [66].

Parathyromatosis

Parathyromatosis is a rare iatrogenic complication that results from the rupture of an adenomatous gland. This causes seeding of hyperfunctioning parathyroid cells and subsequent development of miliary nodules in the exposed soft tissues. When present, this condition is only identified intraoperatively, as the nodules are too small to be detected in preoperative imaging or localization studies [67]. Given its etiology, parathyromatosis is only identified in the context of reoperative parathyroid surgery, and has been described to be more common in patients treated for secondary hyperparathyroidism [68]. From the surgeon's perspective it poses an extremely challenging scenario as the only option for cure is en-bloc resection of the involved tissues, which in most cases only serves as a debulking. Unfortunately, most patients will require long-term medical management after the surgical attempt. Since this an avoidable complication, parathyroid surgeons should be cognizant of the condition and exercise meticulous surgical technique at all times.

Pneumothorax

Pneumothorax is a rare complication of parathyroidectomy. In a report of 4 patients who developed pneumothorax after MIP, extreme neck hyperextension was identified as the common denominator for the cohort [69]. The authors also identified other factors that could place patients at risk, including dissection in the superior mediastinum, traction on the thyrothymic ligament, and a low-lying inferior parathyroid gland [69]. Another report—also in patients undergoing MIP—identified mediastinal adenomas and history of emphysema as potential risk factors [70]. Pneumothorax has also been reported in patients undergoing bilateral neck exploration; Low et al. report a single case in a series of 766 open procedures (0.1 %) [29]. Regardless of the surgical approach, care must be exercised when addressing lesions located low in the neck or in the mediastinum, as the proximity of the pleural apices appears to increase the risk of this complication.

Hungry Bone Syndrome

Hungry bone syndrome (HBS) is an uncommon but potentially devastating complication of parathyroidectomy in the context of primary hyperparathyroidism. It is defined as a profound (serum calcium <2.1 mmol/l), prolonged (beyond the 4th postoperative day) and symptomatic [71] hypocalcemia, commonly associated with hypophosphatemia and hypomagnesaemia, that is observed almost exclusively in patients with severe hyperparathyroidism and high bone turnover. This complication is almost exclusively seen in patients with secondary and tertiary hyperparathyroidism. The etiology of HBS is the rapid incorporation of calcium into bone following an abrupt decline in serum PTH levels and associated osteoclastic bone resorption. In these cases, there is a decrease in activation of new bone remodeling sites in the context of a persistently elevated osteoblastic activity, leading to a rapid increase in bone mass. From the clinical perspective, it is important to differentiate this condition from other causes of postoperative hypocalcemia in patients with primary hyperparathyroidism. In most of these patients, the drop in serum calcium is mild, self-limited, and maximal between the second and fourth postoperative days [72, 73]. Devascularization, surgical trauma or just long-term suppression of the remaining parathyroid glands are plausible causes for prolonged postoperative hypocalcemia; however, in these cases the hypocalcemia will typically not be as severe, and patients will lack the characteristic musculoskeletal manifestations observed in patients with HBS such as *osteitis fibrosa cystica* and *brown tumors*. These bony defects are heraldic of increased osteoclastic activity and their presence should be acknowledged by the clinician prior to surgery.

Patients considered at-risk for developing this condition include those with long-standing disease, high PTH levels [74, 75], large adenomas [76], older age [74], altered bone density or bone pain [77], elevated serum alkaline phosphatase [74], and low levels of vitamin-D [74, 78]. In a recent systematic literature review, Witteveen et al. reports that the incidence of HBS is 25–90 % in patients with any radiological evidence of parathyroid disease vs. 0–6 % in patients without evidence of skeletal involvement [79]. In terms of biochemical risk stratification, several markers have been identified as potential predictors for the development of this condition (Table 46.2). These tests should be requested and interpreted in the context of a comprehensive preoperative evaluation of patients with secondary and tertiary hyperparathyroidism.

The primary treatment of HBS is close monitoring and aggressive supplementation of serum calcium, commonly requiring doses of 6–12 g. of elemental calcium per day [80]. Routinely, intravenous supplementation will be first and subsequently transitioned to oral supplementation. Vitamin-D analogs have been a critical addition to armamentarium for the management of severe hypocalcemia, these drugs should be started promptly and the dose should be escalated liberally. In a similar fashion, serum magnesium should be closely monitored and properly replenished.

Bisphosphonates are part of the pharmacological arsenal against the osteoclast-mediated

Table 46.2 Preoperative laboratory data in patients with primary hyperparathyroidism who developed HBS following parathyroidectomy compared with those who did not Witteveen et al. [79]

Laboratory investigation	Authors	Patients who developed HBS	Patients who did not develop HBS	*P* value
s-Calcium (mmol/l)	Brasier & Nussbaum [74]	3.00±0.05	2.88±0.03	<0.05
	Spiegel et al. [89]	3.25±0.05	3.00±0.03	<0.001
	Heath et al. [78]	3.94±0.38	2.95±0.15	<0.01
	Lee et al. [75]	3.00±0.1	3.00±0.08	0.7
s-PTH (pmol/l)	Brasier & Nussbaum [74]	10.2±2.00	5.7±0.3	<0.05
	Lee et al. [75]	30.7±10	32.9±6	0.2
s-Alkaline phosphatase (U/l)	Brasier & Nussbaum [74]	68±15	38±2	<0.05
	Heath et al. [78]	51±37	12±6	<0.01
	Lee et al. [75]	248±48	169±31	0.1
s-Magnesium (mEq/l)	Brasier & Nussbaum [74]	1.5±0.1	1.7±0.04	<0.001
s-Albumin (g/dl)	Brasier & Nussbaum [74]	3.9±0.1	4.3±0.04	<0.001

bone loss that characterizes several conditions; in light of the common pathogenic pathway with HBS, these agents have been used to prevent the development of this complication. In this regards, several authors have reported a both decreased severity and duration of HBS among patients treated with this family of drugs prior to their surgery [81, 82].

Summary

Complications arising from parathyroid surgery are similar to those from the other chief surgery of the central neck, thyroidectomy. Since in many cases, the patients are not highly symptomatic from their hyperparathyroidism, it is very important to mitigate risks and avoid complications. A unique complication of parathyroid surgery which raises the likelihood of future complications, is the failure to find the offending parathyroid gland(s) which sets the stage for a revision operation.

Society Guidelines: N/A

Best Practices: N/A

Expert Opinion

Although the complications for parathyroid surgery are largely shared with thyroid surgery, the potential most potentially devastating complication is failure to manage the hyperparathyroidism leading to the need for revision surgery.

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Parathyroid Ultrasound: Certification and Accreditation

47

Lisa A. Orloff

Contents

Introduction

Office-based ultrasound has become an important component of many endocrinology and surgical practices that treat parathyroid disease. The skills of performing and interpreting ultrasound are increasingly being taught during otolaryngology and surgery residencies and postgraduate subspecialty training, especially in endocrinology, endocrine, and head and neck surgery fellowships. Additional training is often pursued through 1- to 2-day basic or advanced ultrasound courses, most commonly associated with professional society meetings such as the American College of Surgeons, American Academy of Otolaryngology/Head and Neck Surgery, and American Association of Clinical Endocrinologists.

Expertise in parathyroid ultrasonography is not based on successful completion of a specific training or certification course, but rather is achieved through regular clinical and mentored bedside practice of parathyroid and neck sonography, as well as through participation in continuing medical education didactics. Ultrasound optimization occurs through correlation between preoperative imaging and surgical findings and feedback. Certification courses provide an organized approach to initial and continuing education in ultrasonography for trainees as well as for practicing physicians, but improved sensitivity

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and specificity arise with experience and volume by dedicated clinicians (radiologists, surgeons, and endocrinologists) performing the procedure in practice. In North America, the dominant certification courses are the American College of Surgeons *Thyroid and Parathyroid Ultrasound Skills-Oriented Course* and the American Association of Clinical Endocrinologists *AACE Diagnostic Endocrine Neck Ultrasound and UGFNA Course* ®. Both of these courses are offered at the respective parent organization annual meetings as well as several times throughout the year at exported venues in conjunction with other institutions and professional societies.

History: In 1998, the American College of Surgeons released statement ST-31, supporting the use of ultrasound by appropriately trained surgeons. Similarly, in recognition of ultrasound as a tool to be utilized across medical specialties, the American Medical Association (AMA) drafted a resolution in 2000 affirming that ultrasound imaging is within the scope of practice of appropriately trained physicians [Resolution H-230.960]. The AMA policy on ultrasound imaging affirms that privileging of the physician to perform ultrasound procedures in a hospital setting should be a function of hospital medical staffs and should be specifically delineated on the Department's Delineation of Privileges form. The AMA further states that hospital medical staffs should review and approve criteria for granting ultrasound privileges that are in accordance with recommended training and education standards developed by each physician's respective specialty. Since medical specialty boards range from having very specific US standards to having no defined standards at all, this process can still be somewhat nebulous.

Current Ultrasound Accreditation Option

American Institute of Ultrasound in Medicine

Fortunately, accreditation for parathyroid (and thyroid) ultrasonography has evolved and is currently available for clinicians through two main pathways: the American Institute of Ultrasound in Medicine (AIUM) Practice Accreditation process and the Endocrine Certification in Neck Ultrasound (ECNU) program offered by AACE, and recognized by AIUM.

AIUM ultrasound practice accreditation is a voluntary peer review process that allows practices to demonstrate that they meet or exceed nationally recognized standards in the performance and interpretation of diagnostic ultrasound examinations. Practices accredited by the AIUM have demonstrated competency in the key aspects of ultrasonography, including personnel education, training, and experience; document storage and record keeping; policies and procedures safeguarding patients, personnel, and equipment; instrumentation; quality assurance; and case studies. Practices must also file attestation to satisfactory completion of AIUM physician training guidelines.

Case studies are submitted for review to ensure that appropriate images are obtained and that interpretation is accurate. For dedicated thyroid/parathyroid ultrasound accreditation, case study requirements include a total of four cases consisting of three abnormal diagnostic thyroid/parathyroid cases with corresponding final reports, and one abnormal diagnostic thyroid/parathyroid case with corresponding final report which includes an ultrasound-guided fine-needle aspiration (UGFNA). The UGFNA can be performed on a different date than the diagnostic ultrasound, but must be performed on the same patient and include a separate report for the procedure, and the needle must be shown within the lesion on an image. The diagnostic ultrasound must include transverse and sagittal images and measurements of the right and left thyroid lobes, the isthmus, abnormalities present, parathyroid pathology (if present), and USGFNA (if indicated.)

Alternatively, AIUM accreditation in head and neck ultrasound can be obtained by submitting a total of ten head and neck ultrasound exams with corresponding final reports from at least three of the six general head and neck categories: (1) salivary glands, (2) lymph nodes, (3) congenital lesions, (4) miscellaneous mass lesions, (5) infection and trauma, and (6) endocrine. In this pathway, at least

two of the ten cases must include fine-needle aspiration for cytology. For FNA, image of the needle within the lesion must be demonstrated. Images for each case should be complete and represent salient features sufficient to render an accurate diagnosis. Detailed instructions for applying for AIUM accreditation can be found at http://www.aium.org/accreditation/accreditation.aspx.

Endocrine Certification in Neck Ultrasound

ECNU is a similar pathway to professional certification in the field of neck ultrasonography for physicians, most often endocrinologists, who perform diagnostic ultrasound and UGFNA for thyroid and parathyroid disorders. The ECNU credential signifies that an individual has passed the Comprehensive Certification Examination (CCE) and has successfully completed the Validation of Competency Process (VCP). Participation in the ECNU Program is voluntary and open to anyone meeting the eligibility requirements. Membership in AACE is not required. ECNU is recognized by the AIUM, and allows those with the ECNU credential to be directors of ultrasound laboratories. Also, it is expected that achieving ECNU certification (or direct AIUM accreditation) will become increasingly important in the future for reimbursement from Medicare and third-party payors.

Candidates applying for the ECNU Program may qualify through one of several different routes, including board eligible/board-certified (BE/BC) endocrinologists; BE/BC cytopathologists; BE/BC endocrine surgeons; BE/BC otolaryngologists/head and neck surgeons; BE/BC radiologists; and endocrinology fellows/trainees. Common requirements include having attended CME-accredited, approved basic thyroid ultrasound course(s) worth at least 15.0 h of AMA PRA Category 1 Credits™ within the past 3 years prior to applying to the ECNU Program (10 of the 15 h must come from a comprehensive in-person introductory/basic or advanced ultrasound course that includes both didactic (lecture) and lab sessions with hands-on neck imaging as well as USGFNA instruction on phantoms); be currently performing, interpreting, and documenting at least 100 ultrasound studies per year (70 diagnostic; 30 UGFNA) that include thyroid and parathyroid ultrasound and thyroid cancer lymph node evaluation; and submitting a complete ECNU Program Application.

Summary

More information on the ECNU pathway can be found at https://www.aace.com/ecnu. CME hours for parathyroid ultrasound can be obtained from multiple courses, many of which are also listed and updated on the AACE website.

Best Practices: N/A

Society Guidelines: N/A

Expert Opinion

Ultrasonography is widely recognized as operator dependent, and the success of parathyroid ultrasound is naturally influenced by the motivation of the examiner. Beyond ultrasound education, certification, and accreditation, a conscious effort to correlate ultrasound and surgical findings can contribute to optimizing the outcome of parathyroid ultrasound and the management of hyperparathyroidism.

Reference: N/A

Primary Hyperparathyroidism in the Pediatric Patient

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Introduction

Parathyroid hormone (PTH) is the principal calcium homeostasis-regulating hormone. PTH secretion from the parathyroid gland is stimulated by hypocalcemia, and decreased by hypercalcemia. The regulation of PTH is through an interaction of serum-ionized calcium with calcium-sensing receptors (CaSR) located on the plasma membrane of parathyroid cells. The hallmark of primary hyperparathyroidism (PHPT) is hypercalcemia, which results from the excessive secretion of PTH by one or more of the four parathyroid glands. PHPT occurs as a result of a specific defect in a parathyroid gland. Meanwhile in secondary hyperparathyroidism, the increased secretion of PTH is an adaptive response to low serum levels of calcium or vitamin D. In tertiary hyperparathyroidism, serum levels of PTH and calcium are both elevated—this condition reflects maladaptive and unregulated parathyroid function in response to prolonged parathyroid stimulation by antecedent hypocalcemia, such as in chronic kidney disease.

Presentation of Disease

Primary hyperparathyroidism (PHPT) is a rare disease in infants, children, and adolescents [1, 2]. Prior to 1984, fewer than 150 children with

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Table 48.1 Symptoms of hypercalcemia by organ system

General	Cardiac	CNS	Renal	GI
Decreased bone density	Bradycardia	Fatigue	Nephrocalcinosis	Constipation
Anorexia	Shortened QT interval	Hypotonia/weakness	Nephrolithiasis	Nausea/vomiting
Weight loss	Prolonged PR interval	Seizure	Urolithiasis	Pancreatitis
Pruritus	Arrhythmias	Coma	Polyuria	Ileus

PHPT had been described in the literature [3]. However, since that time, several large pediatric case series have been published that increased the number of reported cases of PHPT in this age group to more than 300 [1–13]. The classic female preponderance of adult PHPT has not been well delineated in the pediatric population. The female:male ratio gap begins to widen starting in the third decade until the perimenopausal age where the ratio remains stable for the next 20 years. PHPT overall has a female 2.8:1 dominance in ratio over men [14]. The overall incidence of the disease is much lower in the pediatric population, 2–5 in 100,000 per year, versus in adults where it affects 1 of 500 women and 1 of 2000 men per year [1, 2, 15–17].

Unlike adult PHPT, which is often found incidentally in asymptomatic patients, childhood PHPT is clinically symptomatic. The majority of pediatric cases typically present with traditional signs or symptoms of hypercalcemia, which can be remembered by the phrase "kidney stones, broken bones, abdominal groans, and psychiatric overtones." These terms refer to nephro- and urolithiasis, metabolic bone disease (which includes reduced bone density, fractures, and osteitis fibrosa cystica), abdominal pain due to constipation or pancreatitis, and neurocognitive or psychiatric dysfunction including lethargy and psychosis (Table 48.1). Pediatric case reports also describe a wide range of additional vague or nonspecific features.

In newborns, there is a very rare homozygous form of familial hypocalciuric hypercalcemia (FHH), caused by hereditary mutation of the CaSR gene [18, 19]. Severe, symptomatic, and often life-threatening hypercalcemia along with increased PTH and relatively low urine calcium is seen and a history of early-onset hypercalcemia in a family member is highly suggestive. Conversely, heterozygotes are often asymptomatic and usually present later in life with incidental hypercalcemia and slightly elevated PTH [20].

In older children and adolescents, PHPT most often develops in isolation and presents as a single adenoma. PHPT can occasionally present secondary to multi-gland disease which is more likely to develop as part of an inherited genetic disorder such as multiple endocrine neoplasia type 1 (MEN1) or type 2A (MEN2A) or familial isolated hyperparathyroidism (Table 48.2).

Parathyroid Development

The total mass of all parathyroid tissue in a newborn is between 6 and 9 mg. The glands are compact, consisting of distinct groups of functionally active chief cells that are heterogeneous in size. The total number of glandular cells in a newborn is about 4.3×10^6 [21]. During the first year of life, the total parathyroid mass increases three- to four-fold. By age 5, their mass increases an additional two-fold, and around age 10, another three-fold. Progressively, total parathyroid mass increases to by 35–50 years of age and then stabilizes until the eighth decade of life [21].

Age-related changes in the parathyroids of children and adolescents include an increase in the number of chief cells and the appearance of oxyphil elements [22]. These changes are paralleled by progressive development of follicular structures lined by chief cells and filled with colloid-like fluid which reacts with amyloid. While stromal fat is a prominent part of normal adult parathyroid histopathology, the stroma of the pediatric parathyroid

Table 48.2 Etiology of primary hyperparathyroidism in pediatric patients

Neonatal severe hyperparathyroidism (NSHPT)	Homozygous form of FHH CaSR mutation. Severe, can be life threatening. Multi-gland disease.
Familial hypocalciuric hypercalcemia (FHH)	Often heterozygotes for CaSR mutations, asymptomatic and diagnosed at any age. Mildly elevated calcium and PTH with low urine calcium.
Familial isolated hyperparathyroidism	Several different mutations, usually autosomal dominant. Usually multi-gland disease but can have adenomas.
MEN-1	PHPT can be presenting symptom. Usually multi-gland disease. Prolactinoma and pancreatic islet cell tumor complete triad.
MEN-2A	Mutation in RET oncogene. Less common to present with PHPT (10–20 %). Medullary thyroid carcinoma and pheochromocytoma.
Sporadic single adenomas	>80 % of PHPT cases in both children and adults. Classically symptomatic. High calcium levels in blood and urine, high or high-normal PTH.
Parathyroid carcinoma	Extremely rare (<1 %). Single gland. High PTH, serum, and urine calcium.

is significantly less adipose. The pediatric parathyroid appears denser with significant development of adipose tissue beginning in puberty. The adipose composition of the glands reaches 10–25 % of total gland mass by age 25–30 and 60–70 % in patients over 80 [21].

Neonatal PHPT

Most patients with familial hypocalciuric hypercalcemia (FHH) are heterozygous for mutations in the CaSR. Generally, these patients are asymptomatic and diagnosed only incidentally. Neonatal severe hyperparathyroidism (NSHPT) is a very rare and severe form of FHH that may present in the neonatal period in patients who are homozygous for this mutation. NSHPT is associated with severe metabolic bone disease and often life-threatening hypercalcemia (e.g., calcium levels >20 mg/dL). The diagnosis of NSHPT relies on the documentation of markedly elevated PTH levels, severe hypercalcemia, and relative hypocalciuria. A family history of early-onset hypercalcemia in a sibling or parent will further substantiate the diagnosis of FHH. It is important to recognize the distinction between NSHPT and the neonatal hyperparathyroidism associated with maternal hypocalcemia, which is transient and occurs in infants born to mothers with either severe vitamin D deficiency or hypoparathyroidism.

In the vast majority of cases that have been analyzed to date, NSHPT has been associated with homozygous inactivating mutations in the *CASR* gene, which encodes the CaSR located at 3p13.3 [23]. CaSR is expressed widely throughout the body, but its most significant physiologic role is the regulation of calcium homeostasis through its expression on the plasma membranes of parathyroid and renal tubule cells. Binding of extracellular calcium ions (Ca^{2+}) to CaSRs leads to activation of signaling pathways that inhibit secretion of PTH by parathyroid cells and enhance urinary calcium excretion in distal renal tubule cells. Most neonates with NSHPT carry inactivating mutations on both *CASR* alleles, which leads to complete or near-complete absence of functional CaSRs in the parathyroid and in other cells in the body. This loss of calcium-sensing ability promotes enlargement of all four of the parathyroid glands and increased secretion of PTH, as well as decreased renal excretion of calcium [23, 24]. Subsequently, severe hypercalcemia results. It is postulated that the exposure of the affected fetus to normal maternal calcium concentrations intensifies development of hyperparathyroidism in utero, and leads to more severe hypercalcemia after birth [25–27].

A recent review article by Roizen and Levine pooled data from several studies on NSHPT. They found nearly equal distribution between males and females. The most common presenting symptoms were skeletal abnormalities (83 %), hypotonia (55 %), failure to thrive/feeding difficulties (43 %), and hyaline membrane disease/respiratory distress (22 %) [3, 8, 28]. Mallet et al.

reported a mean serum calcium level of 3.64 mmol/L with a range of 2.75–6.75 mmol/L (normal range 2.1–2.6 mmol/L) and a mean intact PTH of 36 pg/mL with a range of 56–2214 pg/mL (normal range 10–70 pg/mL) [8]. While historically NSHPT had a mortality rate of nearly 50 %, the advent of automated serum calcium measurements in the 1980s drastically decreased mortality from this disease to nearly zero [3, 8]. Thus, improved outcomes in NSHPT have resulted from the availability of simple assays for serum calcium, and the common practice of measuring serum calcium concentrations in infants who are failing to thrive. In neonates of parents with FHH, early screening of serum calcium allows for rapid diagnosis and early treatment [3, 8].

Childhood and Adolescent PHPT

While genetic syndromes that are associated with multi-gland disease (MGD) are relatively more common to present in patients <40 years of age than in older patients, solitary adenomas remain the most common cause of PHPT in younger patients, and account for over 80 % of primary hyperparathyroidism cases in children and adolescents [29–31]. Multiple gland hyperplasia accounts for only 16–17 % [32]. Double adenomas, normal parathyroid pathology, and parathyroid carcinoma have been reported in the pediatric population, but are exceedingly rare [31]. MGD in younger patients is generally due to hereditary disorders including multiple endocrine neoplasia type 1 (MEN-1), type 2a (MEN-2a), or familial isolated hyperparathyroidism. As discussed earlier, FHH heterozygotes who generally have asymptomatic disease may be diagnosed at any age, often incidentally when having lab work done for other reasons. While there is a well-established association between radiation exposure and later development of PHPT in adults [33, 34], there is only a single case report of childhood PHPT occurring in association with previous therapeutic radiation exposure [35].

Single Adenomas

The number one cause of PHPT in the pediatric population is a single adenoma. Nearly all of these are monoclonal proliferations of benign pathology and arise from sporadic mutations, the molecular basis of which is variable. For example, one subset of parathyroid adenomas is caused by chromosomal rearrangements in which the PTH promoter is placed upstream of cyclin D1 such that the PTH promoter then drives overexpression of this cell cycle regulator resulting in hyperparathyroidism [36].

Childhood and adolescent PHPT usually presents with symptoms, including most notably bone pain and abdominal symptoms such as cramping and constipation. Of the 15 % of patients who report few or no symptoms, the majority of these actually have skeletal or renal pathology. Laboratory tests typically will show classic hypercalcemia, hypophosphatemia, hypercalciuria, and either elevated or inappropriately normal concentrations of intact PTH.

Parathyroid adenomas may originate in any of the four parathyroid glands, but are more common in the inferior glands [37, 38]. Up to 10 % of parathyroid adenomas are found in ectopic sites, including the mediastinum (often within the thymus), thyroid, esophagus, and retroesophageal tissue. Adenomas are usually well circumscribed but lack a definitive capsule [39]. Chief cells are the dominant cell types in the majority of parathyroid adenomas; however, oxyphil cells can also be seen in varying proportions [40, 41] and a few adenomas are comprised exclusively of oxyphil cells [42, 43]. Adenomas are virtually devoid of adipocytes, which are only observed in a rim of the compressed normal parathyroid tissue.

Multi-Gland Disease: Multiple Endocrine Neoplasia and Familial Isolated Hyperparathyroidism

Multiple endocrine neoplasia (MEN) is a group of disorders that cause neoplastic growths in multiple endocrine glands. MEN-1 syndrome, or Wermer's syndrome, affects the parathyroids,

pituitary, and pancreas and is generally associated with multi-gland PHPT, prolactinoma, and pancreatic islet cell tumors. Parathyroid involvement is usually the earliest manifestation of the syndrome and is generally detectable by 20–30 years of age. Treatment for the hyperparathyroidism is four-gland exploration with removal of at least three-and-a-half parathyroid glands. MEN-2a syndrome, or Sipple syndrome, is caused by a mutation in the *RET* proto-oncogene on chromosome 10q11.2. It is associated with multi-gland PHPT, pheochromocytoma, and medullary carcinoma of the thyroid [44]. PHPT is only seen in 10–20 % of patients with MEN2a, and MGD is less common than in MEN1, some patients presenting with a single adenoma [45–47].

Familial isolated hyperparathyroidism can also present with MGD. The majority of cases are inherited in an autosomal dominant pattern; however, a few families show autosomal recessive inheritance. Parathyroid pathology most commonly show chief cell hyperplasia in all four glands; however, some may present with single adenomas. Additionally, there have been reports of an increased risk for parathyroid carcinoma, and other non-endocrine tumors [46–48].

Parathyroid Carcinoma and Hyperparathyroidism Jaw Tumor Syndrome

In adults, parathyroid carcinoma occurs in <1 % of parathyroid tumors and is usually associated with various somatic or germline mutations [49]. The incidence of parathyroid carcinoma in the pediatric patient is even lower. Hyperparathyroidism-jaw tumor syndrome (HPJTS) is a genetic syndrome with a 10–15 % incidence of parathyroid carcinoma and is associated with ossifying fibromas of the mandible and maxilla and, less commonly, renal lesions such as cysts, hamartomas, or Wilms tumors [38, 50, 51]. HPJTS is due to a germline mutation in the tumor-suppressor gene *CDC73* (formerly *HRPT2*). CDC73 mutations have been found in 66–100 % of sporadic parathyroid carcinoma [52].

Imaging

Historically, pretreatment localization was not performed in adults or children with hyperparathyroidism. Intraoperative identification of the diseased gland was performed via bilateral cervical exploration. As imaging techniques have evolved, so has their application in the diagnosis and treatment of parathyroid disease. Most notably, the ability to localize parathyroid adenoma preoperatively using ultrasonography, nuclear medicine scans, computed tomography, and magnetic resonance imaging has ushered in the age of minimally invasive surgical techniques for pediatric patients as well as adults. No single large study has looked at the sensitivity or specificity of different imaging modalities in hyperparathyroidism in children or adolescents. The imaging modality of choice is often extrapolated from studies in adults looking at the same.

Ultrasonography

In 2013, a review by Belcher et al. noted that ultrasound was the most commonly used technique in preoperative localization in the adolescent patient [31]. They report overall good results using ultrasound in adolescents with an average sensitivity of 79 % [31]. An example of ultrasound localization of suspected parathyroid adenoma is shown in Fig. 48.1. Since the 2000's, however, there has been a marked increase in the use of sestamibi nuclear imaging. The same adenoma localized using Tc^{99m}-sestamibi imaging is shown in Fig. 48.2.

Tc^{99m}-Sestamibi Scintigraphy

A study published in 2002 of 287 patients, ages ranging from 13 to 88 years, showed excellent sensitivity of Tc^{99m}-sestamibi scintigraphy for single adenomas [53]. Sensitivity in detecting single adenomas was 96 %; sensitivity for detecting double adenomas and four-gland hyperplasia was 83 % and 45 %, respectively [53]. This study is representative

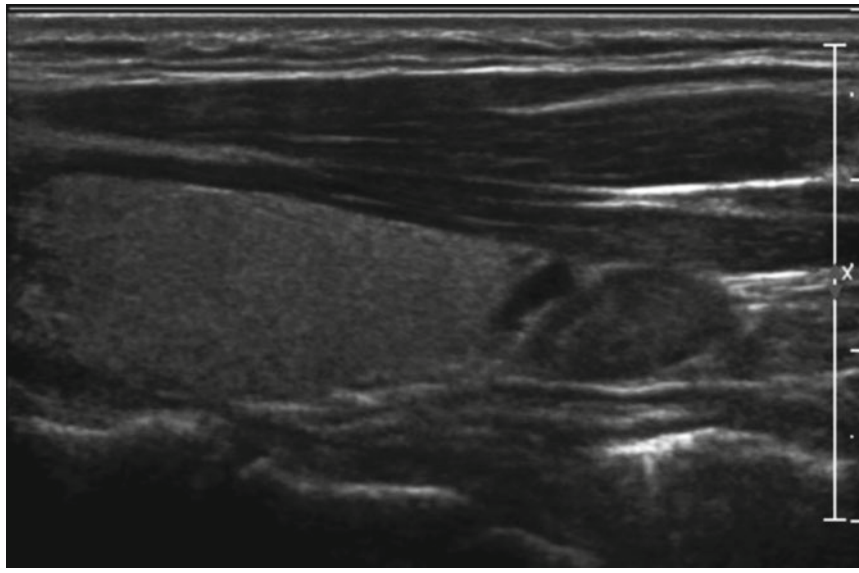

Fig. 48.1 Sagittal view of left parathyroid adenoma using ultrasound without color Doppler

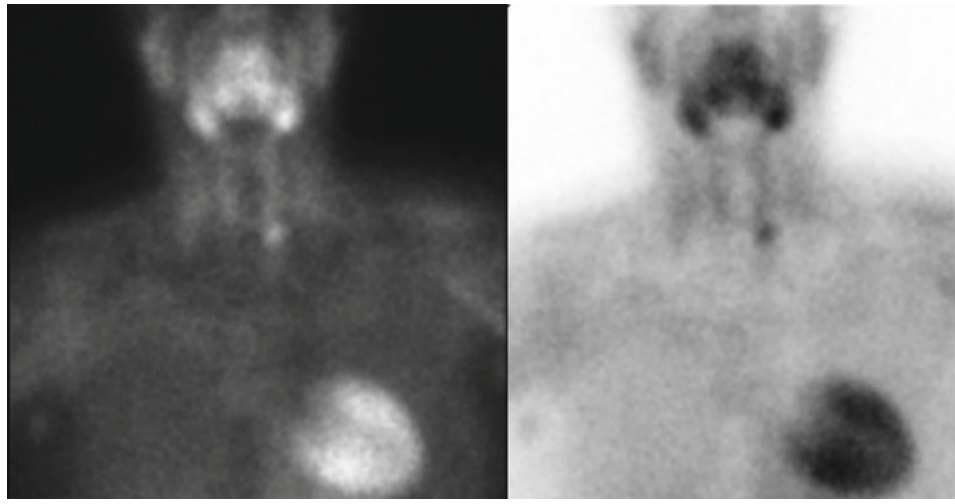

Fig. 48.2 Tc^{99m}-sestamibi scintigraphy in the typical coronal view shows a suspicious left inferior parathyroid gland

of the majority of studies looking at Tc^{99m}-sestamibi scans, showing excellent sensitivity for a single adenoma. The literature regarding the sensitivity of sestamibi specifically in adolescents is lacking, largely due to the rare nature of the disease, but the benefits of its use can be extrapolated.

Computed Tomography and Magnetic Resonance Imaging with Contrast

Typically reserved for use when other modalities fail, CT and MRI may also be effective in localizing parathyroid adenomas. Specifically,

contrast-enhanced three-dimensional studies are best utilized when an ectopic parathyroid is suspected [54]. Thin-section contrast-enhanced CT is reported to have sensitivity ranging from 46 to 87 % for identifying single adenomas [55]. When compared with ^{99m}Tc-sestamibi scanning alone, fusion with CT images allows three-dimensional localization of adenoma, as seen in Fig. 48.3 [56]. The sensitivity of MRI to identify adenomas has been reported to range from 65 to 80 % [55].

Imaging Considerations Unique to Pediatric Patients

Since the mid-1990s, emphasis has been placed on limiting ionizing radiation exposure in children and adolescents. The risks of developing cancer after radiation exposure are multiplied in children for several reasons:

1. Children are considerably more sensitive to radiation than adults.
2. Children have a longer life expectancy than adults.
3. Children may receive a higher radiation dose than necessary if CT settings are not adjusted for their smaller body size [57].

With these considerations, it is no surprise that clinicians are willing to accept a slightly less sensitive test such as ultrasound as the primary mode of localization. There continues to be an increase in the application of Tc^{99m}-sestamibi scanning in children. CT and MRI are therefore typically reserved only when other techniques fail to localize a lesion.

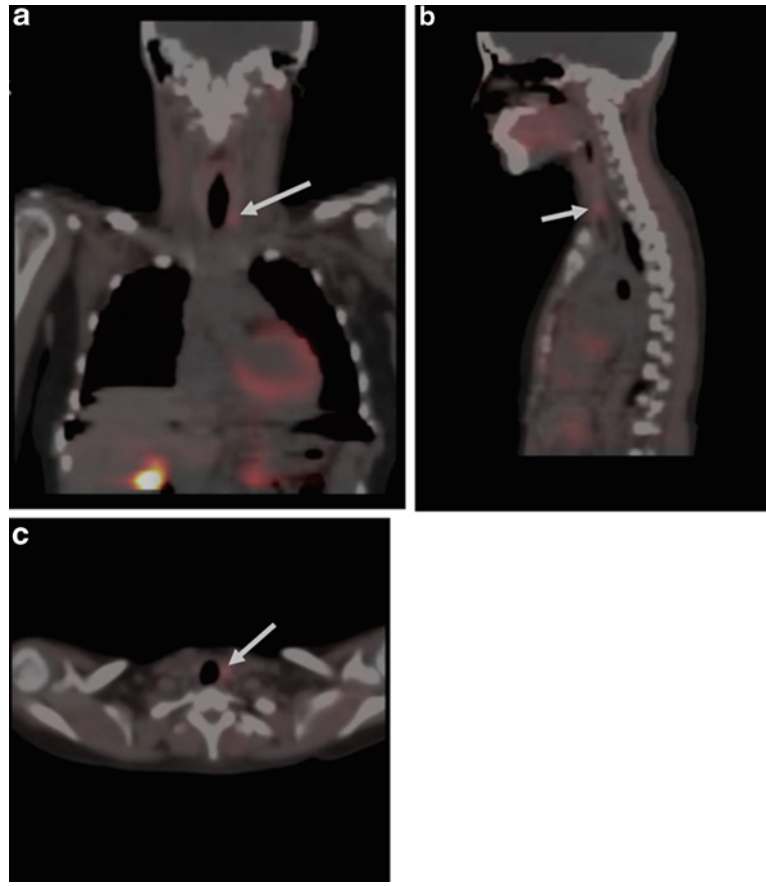

Fig. 48.3 SPECT/CT fusion allows localization of the parathyroid adenoma (*gray arrow*) in the coronal (**a**), sagittal (**b**), and axial (**c**) views. The adenoma was identified in the left inferior parathyroid gland

Treatment

Surgery

Definitive treatment for primary hyperparathyroidism is surgical removal of the offending parathyroid gland or glands. Historically, PHPT in the pediatric population has been managed with a standard bilateral neck exploration with identification of all four glands. This approach continues to be the standard of care for MGD in which at least three-and-a-half glands should be removed for resolution of hypercalcemia. However, with the discovery that PHPT is due to single adenomas in the majority of cases, and with the advent of successful preoperative localization imaging methods such as Tc^{99m}-sestamibi, the trend has been towards minimally invasive surgical exploration with focused excision of a single gland. Norman et al. first described this technique in 1998 [58], and since that time minimally invasive parathyroid surgery (MIPS) has emerged as a leading method of treatment for PHPT caused by single adenoma.

While the literature supporting MIPS in adults is robust, there is currently very little published support for MIPS in the pediatric population. A 2010 paper by Durkin et al. from the University of Wisconsin looked at 25 patients aged 10–25 who underwent surgery for PHPT from 2003 to 2009 [13]. In their series, all children 18 years or younger without a family history of disease were found to have a single adenoma at the time of surgery. MIPS was successful in 78 % of patients with positive preoperative localizing imaging (either Tc^{99m}-sestamibi scanning or ultrasound). Only one patient who was 18 years or younger required conversion to a bilateral exploration, and this patient was found to have single-gland disease on the side contralateral to the positive localization study [13].

MIPS can be achieved through either the standard Kocher incision, a small transverse midline incision, a small transverse incision with endoscopy (either purely endoscopic or video-assisted), or an extra-cervical incision with endoscopy. Intraoperative parathyroid hormone (IOPTH) levels may be measured during the procedure, or a gamma probe used during radio-guided parathyroidectomy, to confirm that the correct gland has been removed and that no further hyperfunctioning tissue remains. MIPS has many advantages in adults including that it can be performed using local anesthesia, requires less operative time, has fewer complications, and offers an improved cosmetic result and greater patient satisfaction [59]. Additional advantages of MIPS are earlier hospital discharge and decreased overall associated costs [58, 59]. The same advantages are likely to be observed in children, except perhaps performing the procedure under local anesthesia.

Medications

Although surgery is the only curative treatment for NSHPT, there have been reports of persistent hypercalcemia in patients who have undergone removal of three-and-a-half glands. In these cases, medical therapy with either intravenous bisphosphonates, or oral type-2 calcimimetics, or both has proved helpful. Bisphosphonates are a class of drugs that encourage apoptosis of osteoclasts by disrupting the HMG-CoA reductase pathway and thereby slow bone resorption [60]. Type-2 calcimimetics, such as cinacalcet, are allosteric modifiers that increase the affinity of the receptor for calcium and thereby reduce the threshold for receptor activation by Ca^{2+}. While the use of bisphosphonates and calcimimetics has not been standardized in pediatric patients for the treatment of hyperparathyroidism, there have been several case reports that suggest their usefulness in delaying or removing the need for surgery in cases of FHH and in cases of NSHPT with a heterozygous mutation in which some CaSR function is preserved [61–66]. Not surprisingly, cinacalcet was not beneficial in a newborn with NSHPT due to homozygous mutations in the *CASR* that cause a complete loss of receptor expression [67]. However, given how rapidly cinacalcet acts in NSHPT [63], it may be reasonable to consider a brief therapeutic trial in affected patients with life-threatening hypercalcemia before proceeding to surgery. Although calcimimetics can reduce serum levels of PTH and are able to control hypercalcemia, the long-term effects of these agents on the skeleton (and other organs) are uncertain and

some animal model studies suggest that these agents may contribute to structural bone disease despite normalizing serum calcium and PTH concentrations [68, 69]. The importance of monitoring serum calcium levels closely during treatment with cinacalcet cannot be overstated. Profound hypocalcemia has resulted in the death of a young patient in a clinical trial and henceforth clinical trials of cinacalcet use in children have been placed on hold [70].

Summary Points

- Primary hyperparathyroidism is caused by a malfunction intrinsic to the parathyroid gland's ability to respond to serum calcium levels appropriately. Therefore, PTH is oversecreted which leads to downstream multiorgan responses to increase serum calcium above the normal level.
- Children are more likely to present with symptoms of hypercalcemia including bone pain from resorption, urolithiasis, nephrolithiasis, and nonspecific signs such as fatigue and muscle weakness.
- Neonatal severe HPT is caused by homozygous mutations of the CaSR gene resulting in complete insensitivity of the cells to activity of calcium. Early diagnosis has drastically improved survivability of this disease.
- PHPT in the pediatric population is most commonly caused by a single adenoma. Multigland disease is often associated with a genetic syndrome such as MEN1, MEN2a, or FHH.
- Ultrasonography, thallium-technetium dual-isotope scintigraphy, and Tc^{99m}-sestamibi scintigraphy have allowed for the localization of the majority of these single adenomas.
- Accurate disease localization has allowed for the development of directed minimally invasive parathyroid surgery as a favorable alternative over the traditional bilateral central neck exploration.
- While the data are sparse regarding MIP in the pediatric population, extrapolating from the risk profile in adults, it seems to offer a less morbid treatment option.

Society guidelines

Bilezikian JP, Khan AA, Potts JT Jr, on behalf of the Third International Workshop on the Management of Asymptomatic Primary Hyperthyroidism: 2009 Summary Statement: Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Third International Workshop, J Clin Endocrinol Metab 94:335–339.

Best Practices: N/A

Expert Opinion

Pediatric hyperparathyroidism is a relatively rare condition. Awareness of the symptomatology for hyperparathyroidism is necessary to be able to include this disorder in a differential for potential pathophysiology. It is important to determine if PHPT is sporadic versus part of an inherited syndrome, as this may have bearing on what surgical intervention and extent of surgery would be considered. A comprehensive history including family history is critical in order to help determine which patients may require preoperative genetic testing.

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