

Supplementary Online Content

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eAppendix. The American Association of Endocrine Surgeons (AAES) Guidelines for Definitive Management of Primary Hyperparathyroidism

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This supplementary material has been provided by the authors to give readers additional information about their work.

ABSTRACT

Importance Primary hyperparathyroidism (pHPT) is a common clinical problem for which the only definitive management is surgery. Surgical management has evolved considerably during the last several decades.

Objective To develop evidence-based guidelines to enhance the appropriate, safe, and effective practice of parathyroidectomy.

Evidence Review A multidisciplinary panel used PubMed to reviewed the medical literature from January 1, 1985, to July 1, 2015. Levels of evidence were determined using the American College of Physicians grading system, and recommendations were discussed until consensus.

Findings Initial evaluation should include 25-hydroxyvitamin D measurement, 24-hour urine calcium measurement, dual-energy x-ray absorptiometry, and supplementation for vitamin D deficiency.

Parathyroidectomy is indicated for all symptomatic patients, should be considered for most asymptomatic patients, and is more cost-effective than observation or pharmacologic therapy. Cervical ultrasonography or other high-resolution imaging is recommended for operative planning. Patients with nonlocalizing imaging remain surgical candidates. Preoperative parathyroid biopsy should be avoided. Surgeons who perform a high volume of operations have better outcomes. The possibility of multigland disease should be routinely considered. Both focused, image-guided surgery (minimally invasive parathyroidectomy) and bilateral exploration are appropriate operations that achieve high cure rates. For minimally invasive parathyroidectomy, intraoperative parathyroid hormone monitoring via a reliable protocol is recommended. Minimally invasive parathyroidectomy is not routinely recommended for known or suspected multigland disease. Ex vivo aspiration of resected parathyroid tissue may be used to confirm parathyroid tissue intraoperatively. Clinically relevant thyroid disease

should be assessed preoperatively and managed during parathyroidectomy. Devascularized normal parathyroid tissue should be autotransplanted. Patients should be observed postoperatively for hematoma, evaluated for hypocalcemia and symptoms of hypocalcemia, and followed up to assess for cure defined as eucalcemia at more than 6 months. Calcium supplementation may be indicated postoperatively. Familial pHPT, reoperative parathyroidectomy, and parathyroid carcinoma are challenging entities that require special consideration and expertise.

Conclusions and Relevance Evidence-based recommendations were created to assist clinicians in the optimal treatment of patients with pHPT.

INTRODUCTION

The surgical treatment of primary hyperparathyroidism (pHPT) has undergone extensive change in the last two decades. Laboratory testing, point of care access, radiographic imaging, operative techniques, intraoperative adjuncts, and other areas of surgical care have all rapidly evolved. With these transformations has come significant potential for subjective interpretation and variable management. Recognizing these innovations and challenges, the American Association of Endocrine Surgeons (AAES) determined the need to develop evidence-based clinical guidelines to enhance the safe and effective practice of surgery to achieve definitive treatment of pHPT. Intended for surgeons who perform parathyroidectomy, as well as their team members, these guidelines supply a broad medical update on the clinical spectrum of pHPT and in addition specifically aim to:

- 1) Provide surgical caregivers with a current background understanding of the epidemiology and pathogenesis of pHPT.
- 2) Outline the process for diagnosis of pHPT by laboratory studies and clinical manifestations (both subjective and objective) and once a diagnosis is established, examine the indications for surgical intervention.

- 3) Detail the pre- and intra-operative management of pHPT including creation of a patient-specific operative plan based on available resources, surgeon experience, and patient characteristics.
- 4) Delineate methods for safe and effective postoperative management including a definition of cure and an algorithm for managing operative failure.

pHPT is a common clinical problem for which the only definitive management is surgical intervention. The presentation, diagnosis and medical management have recently been addressed in several influential statements including the National Institutes of Health (NIH) consensus development conference on diagnosis and management of asymptomatic primary hyperparathyroidism¹, the American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons guidelines for the diagnosis and management of primary hyperparathyroidism², and several international workshops³⁻⁵, which offer selected surgical suggestions as a portion of their content. The guidelines presented here specifically focus on the surgical management of pHPT with the goal of achieving cure as safely and efficiently as possible.

METHODS

Writing Group, Topics, and Analysis of Literature Evidence

With the approval of the AAES Council at the project's inception, a multidisciplinary panel of endocrinologists, pathologists, surgeons and radiologists was appointed by the AAES President to include broad-based complementary expertise. Eleven of the 16 writing group members have been AAES presidents, officers or council members. In January 2014, individual writing subcommittees were established for each of 17 topics and were comprised of 2-5 coauthors. Topic outlines were vigorously discussed to consensus.

Search parameters for the worldwide medical literature were set from January 1985 to July 1, 2015 (30 years of the most recent data and research available in the field). At the discretion of the authors, this time frame was expanded to allow for inclusion of "classic literature" i.e. large and/or landmark articles to give historical reference or to illustrate time-tested principles of management. For each topic, the primary co-author then conducted a PubMed Medical Subject Heading (MESH) search using Boolean logic for MESH terms. Limitations were applied to select publications containing an abstract (English Language) and published in

abridged index medicus (AIM), otherwise known as core clinical journals in PubMed. Results yielded a broad category of publication types which were then critically appraised to generate a pertinent bibliography. Particular value was assigned to study design (e.g. randomized controlled trials (RCT), meta-analyses and large single-center reports).

Text and Recommendations

To craft the specific content, all topics went through a rigorous process of determining the quality of the evidence, drafting text and recommendations supported by evidence, and amending that material in discussion to consensus. The draft document was discussed in detail during regular teleconferences as well as by email and in person. Expert opinion was vigorously examined. Editing to eliminate redundancy, verify referenced data, and ensure that the material met the guiding principles was performed by 5 committee members (SMW, TSW, DTR, JAL, and SEC).

Grading of Practice Recommendations

The writing group adopted the American College of Physicians (ACP) grading system for evidence-based clinical guidelines, which employs a validated scale to critically interpret and evaluate the strength and quality of the evidence⁶. The ACP writing guidelines were drafted in 1981 and have undergone periodic revisions; the most recent version from 2010 was utilized. In brief, the ACP system applies the designations “Strong” when benefits clearly outweigh risks and/or the recommendation should be applied to all or most patients without reservation, “Weak” when benefits are finely balanced with risks or appreciable uncertainty exists, and “Insufficient” when the evidence to support a recommendation is conflicting, lacking, or of poor quality; in these circumstances the writing group provided recommendations based on expert interpretation of the available data. Quality assessment is followed by a formal interpretation about the evidence strength to provide guidance on how to best apply the recommendation to individual patients; evidence quality is graded “High” for well-done RCT or overwhelming evidence, “Moderate” for RCT with important limitations, well-designed cohort or case-control studies, or large observational studies, and “Low” for potentially biased, small observational, or case studies.

AAES and Peer Input

Formal feedback and suggestions were sought from an independent group of non-author AAES experts. Input in development was also sought from AAES membership by online survey in October 2015. We also reviewed comments received after oral presentations on May 18, 2015 at the national AAES meeting in Nashville, Tennessee, and August 25, 2015 at the meeting of the International Association of Endocrine Surgeons in Bangkok, Thailand. Constructive feedback and suggestions from all sources were discussed by the writing group and consensus revisions made to the manuscript as required.

Cautions to Implementation

These guidelines present a process for the surgical evaluation and treatment of pHPT based on current and historical evidence available in the literature at the time of writing. As such, the content may change in the future and it is the responsibility of treating physicians to maintain a current working knowledge of the management of pHPT as it pertains to their practice. The guidelines do not represent the only approach to the management of pHPT, are intended to be flexible, and are not meant to replace an individual physician's judgment. An ultimate determination regarding application should be made by the treating health care professional with full consideration of the individual patient's clinical history and physical status. Adherence to the guidelines is not mandatory and may require significant adaptation in practice settings characterized by barriers to implementation. Moreover, national clinical practice guidelines do not constitute a legal standard of care⁷. Finally, this guideline is intended for the management of pHPT in adults and should not be applied to surgical management of children (<18 years old).

This guideline is based on the established literature and the expert opinions of the writing group, which had complete independence from AAES in its production. No funding was received by the authors or AAES to support this work. Writing group members were asked to disclose any conflicts of interest during the development process and none were identified for any author.

RECOMMENDATIONS

Table 1 outlines the location and title of the individual topics, summarizes the specific recommendations for each topic, and gives the strength of each recommendation based on the ACP grading scale.

1. DIAGNOSIS AND EVALUATION

Primary hyperparathyroidism (pHPT) is a relatively common disorder arising from autonomous overproduction of parathyroid hormone (PTH) by abnormal parathyroid gland(s) and characterized by the repeated elevation of total serum calcium levels with corresponding elevation or inappropriately normal (i.e., nonsuppressed) PTH levels. The diagnosis of pHPT is biochemical.

Clinical Subsets of pHPT

Symptomatic versus Asymptomatic

The onset of pHPT may be insidious because the clinical presentation is heterogeneous and the associated symptoms overlap with those of natural aging and disease. The symptom spectrum of pHPT ranges from having no recognizable symptoms to profound physical and mental disability.

Patients with symptomatic pHPT have overt signs and symptoms directly attributed to the disease. The classic manifestations include nephrolithiasis, osteitis fibrosis cystica, peptic ulcers, and psychiatric/cognitive symptoms. However, the definition of symptomatic disease is still evolving, with the recognition of various neurocognitive, psychiatric, and cardiovascular manifestations that may be attributed to pHPT. In contrast, patients with “asymptomatic” pHPT have no disease-specific symptoms. Prior to routine serum calcium testing, the diagnosis of pHPT was suspected only after the development of clinical symptoms, signs, or features. However, pHPT now is usually detected prior to the development of symptomatic kidney and bone disease.

Hypercalcemic versus Normocalcemic

Hypercalcemic pHPT is characterized by serum calcium levels above the normal range with a concomitant inappropriately high PTH level and is the most commonly recognized presentation of pHPT. In contrast, “normocalcemic pHPT” is a recently recognized, incompletely characterized variant that presents with inappropriately high PTH levels and normal total and ionized serum calcium levels (discussed below).

Establishing the Diagnosis: Laboratory testing

Calcium

In pHPT, patients may have normal total and/or ionized calcium levels at some points during their disease, but will be hypercalcemic the majority of the time; thus, repeated measurements of albumin-corrected calcium levels are usually required for accurate diagnosis.⁸⁻¹³ In healthy patients, approximately 50% of total calcium is ionized, 10% is bound to anions (bicarbonate, citrate, etc.), and 40% is bound to proteins (90% is bound to albumin).⁹ Total serum calcium levels can be corrected for abnormal serum albumin levels using this equation:

Corrected calcium (mg/dL) = (0.8 [4.0 – patient's albumin (g/dL)]) + total calcium (mg/dL).

[Of note, the SI (International System of Units (French: *Système International d'Unités*) unit correction requires calcium levels to be input in mmol/L (normal calcium level is 2.1-2.6 mmol/L which corresponds to 8.5-10.1mg/dL) and albumin to be reported in g/L.]

Although pHPT and malignancy are the two most common causes of high serum calcium levels in adults, other alternate causes of hypercalcemia should be considered in pHPT diagnosis. These include circumstances such as prolonged tourniquet time during blood draws. Non-parathyroid causes of hypercalcemia, however, are associated with suppressed PTH levels. Parathyroid hormone-related peptide (PTHrP) can stimulate the same receptor as PTH. As a result, tumor secretion of PTHrP can lead to excessive bone resorption and hypercalcemia and a PTHrP level may be useful in evaluating hypercalcemia in patients with a history of malignancy.¹⁰ Other causes of hypercalcemia include 1-25-dihydroxyvitamin D production, osteolytic metastases, prolonged immobilization, sarcoidosis, excess calcium ingestion and rarely, ectopic PTH production.

Ionized calcium is detected by calcium-sensing receptors on the surface of parathyroid cells. In the normal state, reduction in ionized calcium levels prompts the synthesis and secretion of PTH.¹¹ Patients with normocalcemic pHPT will have normal serum and ionized calcium levels. For this reason, measurement of ionized calcium levels is necessary to establish the diagnosis of normocalcemic, but not hypercalcemic,

pHPT.^{10,12,13} Secondary causes of a high PTH level should be ruled out prior to the diagnosis of normocalcemic pHPT (Table 2).

Parathyroid Hormone

In patients with pHPT, PTH levels are high or inappropriately normal (i.e. not suppressed in the setting of hypercalcemia). Patients who are on medications known to increase calcium and/or PTH levels (e.g. thiazide diuretics, lithium) can discontinue those medications, if medically appropriate, and undergo repeat biochemical evaluation after approximately 1-3 months. If the biochemical evaluation is unchanged, the medications are unlikely to be the source of the hypercalcemia and can be reintroduced. PTH levels that are in the lower range of normal (<25-30 pg/mL for 1st and 2nd generation intact assays) are more challenging to interpret, but are thought to be abnormal and inappropriately elevated in the setting of hypercalcemia. In these patients, the low-normal PTH levels may be secondary to fragments of PTH not detectable by current PTH assays and/or may represent an early form of pHPT.¹⁴⁻¹⁷

25-Hydroxyvitamin D (25-OH vitamin D)

There is an inverse relationship between 25-OH vitamin D and PTH. Under normal physiologic conditions, vitamin D deficiency and hypocalcemia will both trigger increased production of PTH. In pHPT, 25-OH vitamin D deficiency has been associated with more significant hypercalcemia, more severe bone disease, and increased parathyroid adenoma weight.¹⁸⁻²¹ Measurement of 25-OH vitamin D is the best available test to assess adequacy of vitamin D and should be obtained in all patients being evaluated for pHPT.^{12,18}

Other Diagnostic Labs

Serum creatinine is an important diagnostic tool in patients with pHPT, as the kidney helps to regulate serum levels of calcium and phosphate. The National Kidney Foundation Kidney Diseases Outcomes Quality Initiative (KDOQI) recommends that estimation of glomerular filtration rate (GFR) be based on age, gender, race, weight, and serum measurements of creatinine, albumin, urea, and nitrogen. A GFR <60 cc/min corresponds to Stage 3 chronic kidney disease and has been associated with increased PTH and with increased parameters of bone resorption.^{22,23} Serum phosphate levels are low in nearly half of patients with pHPT. Bone

specific alkaline phosphatase is a marker of bone turnover that can be useful in evaluating the extent of bone disease.^{24,25}

- **RECOMMENDATION 1-1:** The biochemical evaluation of suspected pHPT should include serum total calcium, PTH, creatinine, and 25-OH vitamin D levels.

Strong Recommendation – Moderate quality evidence

Laboratory Testing: Urine

The 4th International Workshop on the Management of Patients with Asymptomatic Hyperparathyroidism recommends obtaining a 24-hour urinary calcium level in all patients suspected to have pHPT.³ A urinary calcium excretion >400 mg/d should be followed by an evaluation of stone risk.

The urinary calcium level is also important to distinguish hypercalcemia of pHPT from that of familial hypocalciuric hypercalcemia (FHH), an autosomal dominant caused by mutations in the renal calcium sensing receptor. FHH is a benign condition of lifelong hypercalcemia and hypocalciuria that rarely requires treatment. Unrecognized FHH can be a cause of unnecessary parathyroid surgery. FHH should be considered in patients with urinary calcium levels <100 mg/24 hours and can be differentiated from pHPT by calculation of the calcium/creatinine clearance ratio (CCCR):

$$\text{CCCR} = (24\text{-hr Ca}_{\text{urine}} / \text{Ca}_{\text{serum}}) / (24\text{-hr Creatinine}_{\text{urine}} / \text{Creatinine}_{\text{serum}}).$$

The threshold CCCR for diagnosing FHH is <0.01, whereas a CCCR >0.02 is diagnostic of pHPT.^{13,26,27} In patients with a CCCR between 0.01 – 0.02, it is important to exclude other causes of hypocalciuria, including use of thiazide diuretics, 25-OH vitamin D deficiency and renal insufficiency.¹⁸ In patients with deficient 25-OH vitamin D levels and a CCCR<0.001, a repeat urinary calcium level should be obtained after repletion to help diagnose or exclude FHH.

- **RECOMMENDATION 1-2:** A 24-hour urine measurement of calcium and creatinine should be considered in patients undergoing evaluation for possible pHPT.

Strong Recommendation - Moderate quality evidence

Normocalcemic pHPT

As stated above, this condition is not well characterized. Although its prevalence is unknown, it is being recognized with increasing frequency. The diagnosis requires exclusion of other causes of secondary PTH elevation (Table 2). In some patients (up to 16%) the condition may progress over time to hypercalcemic pHPT²⁸. An ionized calcium level should be obtained in all patients with suspected normocalcemic pHPT but is not necessary to make the diagnosis of pHPT in hypercalcemic patients.²⁹

Investigation of Symptoms, Features, and Complications of pHPT: Medical History

Symptoms

Although the majority (up to 80%) of patients with pHPT now present with what has been called ‘asymptomatic’ disease, some patients still present with target organ involvement. Symptomatic nephrolithiasis is present in 15-20% of patients with pHPT; up to 10% have recurrent calcium stone disease and up to 12% may have ‘silent nephrolithiasis’.^{30,31} The classic skeletal involvement, osteitis fibrosa cystica, is now rare, although patients may present with fragility fractures (unrelated to significant trauma) due to bone loss. A careful history for nephrolithiasis, fragility fractures, or known osteopenia/osteoporosis should be performed. Patients should also be asked about symptoms related to other sequelae of pHPT, such as gastroesophageal reflux disease (GERD) and in cases of severe hypercalcemia, acute pancreatitis.

Classic neuromuscular symptoms related to pHPT, which include proximal muscle weakness and muscular atrophy, are now rare, although many contemporary patients do report subjective complaints of easy fatigability and generalized weakness.³²⁻³⁵ Similarly, while classic neuropsychiatric symptoms of pHPT, including mental status changes, obtundation, and frank psychosis are uncommon, psychological and cognitive changes, including fatigue, depression, anxiety, emotional lability, sleep disturbances, worsening memory, and inability to concentrate, are now often reported.^{13,34-42} Subjective reporting of these symptoms should be documented, as they may be an indication for surgery and may resolve after curative parathyroidectomy (Section 3).

Family History

Although the majority of patients will have sporadic disease, in 3-5% of patients, pHPT occurs as a component of an inherited syndrome, with specific types including familial isolated pHPT, multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2A (MEN2A), hyperparathyroidism-jaw tumor syndrome (HPT-JT), and FHH.⁴³⁻⁴⁶ Therefore a careful and focused family history should be obtained, for a history of previous neck surgery, kidney stones, pituitary tumors, peptic ulcers, hypercalcemia, or pancreatic tumors.⁴⁷ Since the presence of FHH or an inherited endocrine tumor syndrome affects both the need for surgery and the procedure performed (Section 9), a history of these conditions should be carefully sought.

Personal History

Prior irradiation to the cervical region is thought to be a risk factor for later development of pHPT. Decades ago, external beam radiation was used for benign conditions of the head, neck, and upper chest, such as acne or tonsillar enlargement. While this practice has largely ceased, external beam radiation is still utilized in the treatment of malignant conditions such as breast cancer, lymphoma, and head and neck cancer. In addition, the general population may be unexpectedly exposed to radiation by events such as the Chernobyl nuclear disaster. In patients with pHPT and a history of radiation exposure, the onset of parathyroid disease typically has a latency of 25-40 years after initial exposure.^{48,49} Radioactive iodine, used for treatment of Graves' disease and thyroid cancer, also has been shown to be a risk factor for pHPT.⁵⁰ Since prior irradiation is also associated with differentiated thyroid cancer, the presence of thyroid nodules requiring additional evaluation can affect the conduct of parathyroidectomy and should be carefully investigated preoperatively (Section 11).

Since some medications can cause a biochemical picture mimicking pHPT that may resolve with discontinuation, it is important to ask about these agents. Lithium is thought to directly affect parathyroid tissue by decreasing the sensitivity of the parathyroid cell to calcium, thus altering the set point for PTH secretion.^{51,52} Patients with lithium-associated pHPT may be more likely to have multiglandular disease (MGD) than patients with sporadic pHPT.^{53,54} Thiazide diuretics, which can uncover mild pHPT, are associated with hypercalcemia that may be secondary to a reduction in urine calcium excretion, increased intestinal calcium absorption, or metabolic alkalosis from diuretic use.⁵⁵

- **RECOMMENDATION 1-3:** In patients with suspected pHPT, a personal and family history should be performed.

Strong Recommendation – Moderate quality evidence

Investigation of Symptoms, Features, and Complications of pHPT: Imaging for Detection of End-Organ Disease

Renal Imaging

Recent data suggest that patients with otherwise asymptomatic pHPT may have prevalent nephrocalcinosis and ‘silent’ nephrolithiasis, and that abdominal imaging for detection of small renal calculi is useful. Renal ultrasonography and/or non-enhanced computed tomography (CT) are preferred modalities, although abdominal x-ray can also be obtained.^{31,56,57} In patients with otherwise asymptomatic pHPT, the presence of radiologic nephrolithiasis represents an indication for parathyroidectomy.²⁵

- **RECOMMENDATION 1-4:** In patients with “asymptomatic” pHPT, abdominal imaging should be obtained for detection of nephrocalcinosis or nephrolithiasis.

Weak recommendation - Low quality evidence

Bone Density Examination

As a consequence of the increased bone turnover induced by high PTH levels, pHPT results in site-specific reduction in bone mineral density (BMD), and may predispose to fragility fractures.^{25,58,59} BMD is measured most commonly by dual-energy X-ray absorptiometry (DXA). The World Health Organization defines osteopenia as a reduction in BMD between 1.0 – 2.5 standard deviations below peak bone mass (T-scores between -1.0 and < -2.5) and osteoporosis as a reduction of BMD equal to or greater than 2.5 standard deviations (T-score \leq -2.5). Bone loss on DXA in pHPT is typically greatest at the forearm (one-third distal radius site), as this site is comprised primarily of cortical bone, and least at the lumbar spine, composed primarily of trabecular bone.^{25,59} Recent studies have shown that DXA measurement of the lumbar spine may

overestimate bone strength, underscoring the importance of DXA measurement at multiple sites. BMD should routinely be obtained at three sites: lumbar spine, hip, and distal 1/3 of the radius. Examination should occur within 2 years prior to initial surgical evaluation; interpretation and management of findings should be done in conjunction with the patient's endocrinologist and/or primary care provider.²⁵

- **RECOMMENDATION 1-5:** Bone mineral density should be measured at the lumbar spine, hip, and distal radius, preferably using DXA.

Strong recommendation - High quality evidence

Investigation of Symptoms, Features, and Complications of pHPT: Role of genetic counseling

In pHPT patients with a hereditary syndrome, the extent of parathyroidectomy is affected by the presence of a mutation and by the specific mutation identified (Section 9).^{44-46,60-65} Referral for genetic counseling is essential in patients for whom there is preoperative suspicion of an inherited syndrome. The writing group reached strong consensus that patients <40 years of age at the time of surgery for pHPT be considered for genetic counseling.

MEN1

MEN1 is typically characterized by the occurrence of parathyroid, pancreatic islet, and anterior pituitary tumors, although patients can also manifest neuroendocrine tumors of the thymus or bronchus, adrenal adenomas, lipomas, and axillary skin tags.^{46,66-68} An autosomal dominant disorder, it is estimated that 1-18% of patients with pHPT have MEN1; conversely, the penetrance of parathyroid disease in patients with MEN1 is >95% and is the most common feature of the syndrome.⁴⁶ Patients with MEN1 typically present with parathyroid disease in the third decade, i.e. earlier than the onset of disease in patients with sporadic pHPT. The optimal age to consider genetic testing for MEN1 in patients with pHPT is still, unknown.^{46,47,60,69} Current practice guidelines suggest that all patients with pHPT <30 years or MGD be tested for a *MEN1* gene mutation.⁴⁶

Rare patients with a MEN1-like clinical picture lack mutations in the *MEN1* gene but instead harbor mutations in the CDKI genes *CDKN1B/p27^{Kip1}* or *CDKN2C/p18^{INK4C}*. This newly recognized disorder is termed MEN4. MEN4 patients present with parathyroid involvement, and less frequently with pituitary adenomas and other endocrine features.⁷⁰

MEN2A

Among the MEN2A-associated endocrinopathies, pHPT has a penetrance of 15-30%, compared to >90% for medullary thyroid cancer and 40-50% for pheochromocytoma. There is a strong genotype – phenotype relationship in MEN2A and the specific *RET* mutation can be used to estimate the likelihood of pHPT. In patients with a known *RET* mutation, screening surveillance for pHPT should be performed annually at the time of screening for pheochromocytoma and should include albumin-corrected calcium (with or without PTH levels). Evaluation should occur by the age of 11 years in patients with *RET* mutations in codons 634 and 883 (“high risk”), and by age 16 in patients with other *RET* mutations (“moderate risk”).⁴⁵

Hyperparathyroidism – Jaw Tumor Syndrome (HPT-JT)

CDC73 (previously termed *HRPT2*) is a tumor suppressor gene that encodes parafibromin. A mutation in *CDC73* typically leads to loss of parafibromin expression and is associated with HPT-JT, familial isolated hyperparathyroidism and parathyroid carcinoma. HPT-JT is an autosomal dominant disorder, characterized by both benign and malignant parathyroid disease, fibromas of the mandible and maxilla, renal tumors, and uterine tumors. The average age of onset is not well-established, with recent studies demonstrating a median age of diagnosis of pHPT in the second or third decade.^{63,64} Current recommendations for mutation analysis of *CDC73* include all patients with parathyroid carcinoma, and when MEN1 mutation analysis is negative in patients suspected to have inherited forms of pHPT, namely young patients and those with multigland disease (MGD).^{13,64}

- **RECOMMENDATION 1-6:** Genetic counseling should be performed for patients <40 years of age with pHPT and multigland disease (MGD), and considered for those with a family history or syndromic manifestations.

2. EPIDEMIOLOGY AND PATHOGENESIS

Epidemiology

The reported prevalence of pHPT depends upon the criteria used to define pHPT and the methodology for biochemical screening. The prevalence of hypercalcemia from large population-based Swedish studies ranged from 0.3% to 0.7% of the total population, which increased to 1.3% to 3% in menopausal women.^{71,72} These studies measured serum calcium alone without confirmation of PTH level or albumin testing for biochemical correction. Paradoxically, in Norway the prevalence with PTH testing ranged from 3.6% to 13.9% in postmenopausal women.^{73,74} Altogether, the population-based Scandinavian reports show that pHPT is more common in women and in the elderly. This finding was further validated by studies from Denmark,⁷⁵ Taiwan,⁷⁶ Scotland,⁷⁷ and Switzerland.⁷⁸ In other studies that utilized ionized calcium and PTH testing, the estimated prevalence approximated 3% in postmenopausal women.^{79,80}

The diagnostic rate of pHPT increased in the 1970's when automated routine calcium testing became available. Previously, the diagnosis was largely limited to patients with nephrolithiasis and bone disease.⁸¹ With the introduction of the multichannel autoanalyzer, the percentage of patients diagnosed with subclinical HPT markedly increased. Most of these patients had mild hypercalcemia. One referral center reported a decline in incidence of pHPT in the 1990's,⁵⁵ and then an increase in diagnosis at the time that national osteoporosis screening guidelines were introduced.⁸² These observations suggest case ascertainment bias rather than true shifts in incidence.

The prevalence of pHPT tripled between 1995 and 2010 in a large health care network database in Southern California, from 76 to 233 per 100,000 women and from 30 to 85 per 100,000 men.⁸³ Both incidence of pHPT and the gender disparity increased with advancing age and the age-adjusted incidence was highest among African-Americans. A current study estimated that the prevalence of pHPT is 0.86% of the general population.³⁸ Interestingly, using the electronic medical record, the authors found that only 32% of

hypercalcemic patients were evaluated further with a concomitant PTH assessment. Only 1.3 % of patients with elevated serum calcium had a documented elevation in PTH, and of those, only 17% of patients with biochemical confirmation of disease were treated with parathyroidectomy. Overall, these studies emphasize that despite contemporary assessment, pHPT is under-diagnosed and undertreated.

Although the definitions and methodologies of biochemical testing have been inconsistent in epidemiologic studies, the totality of evidence suggests the incidence of pHPT increases with age, is approximately 2 to 3 times higher in women than in men, and has a prevalence of approximately 1% in postmenopausal women.

Pathologic Features

Safe and effective parathyroidectomy requires mastery of the anatomic and pathophysiologic details reviewed in this section.

Normal parathyroid glands weigh approximately 20-50 mg.⁸⁴ The autonomous hormonal hypersecretion of pHPT may be due to hyperfunction of one or more parathyroid glands, and is affected by one of three different pathologic conditions: adenoma, hyperplasia, or carcinoma. It is expedient to broadly characterize parathyroid pathology as either single gland disease or MGD. Together, double adenomas and hyperplastic glands comprise the multiglandular manifestations of disease. MGD frequencies are reported at 6-33% and the totality of evidence suggests a rate that approximates 15%.^{49,85-97} Regional variability in MGD rates exists.⁹⁸ The majority of cases of pHPT are due to a single benign parathyroid adenoma, and a small percentage is due to a solitary parathyroid carcinoma.

- **Parathyroid adenomas** are benign, well-delineated, often encapsulated, monoclonal neoplasms with scant stromal fat. Gross or microscopic evaluation may reveal a rim of normal adjacent parathyroid tissue. The majority of pHPT cases are due to adenomatous disease of a single parathyroid gland.

- **Double adenomas** are uncommon and difficult to discern from asymmetric MGD. Reports of double adenomas suggest a range in incidence from 2-15%.^{40,47,88-90,96,99-101} Double adenomas may be found in any anatomic configuration, but have a predilection for the superior locations.¹⁰²

- **Parathyroid cysts** are rare lesions that are usually nonfunctional and may be found in up to 3% of parathyroidectomy patients.¹⁰³

- **Parathyroid hyperplasia** is characterized by an increase in cellularity in multiple glands, in contrast to parathyroid adenomas, which typically involve a single gland. Reports suggest that 2-20% of pHPT cases are due to multiglandular parathyroid hyperplasia.¹⁰⁴ Up to 26% of patients with MGD at surgery may have MEN1.⁴⁷

- **Parathyroid carcinomas** are rare malignant tumors responsible for less than 1% of pHPT cases. Gross firmness, cystic features and greyish discoloration or histologic evidence of tumor invasion are the principal features of parathyroid carcinoma (Section 12.)

- **RECOMMENDATION 2-1:** MGD affects approximately 15% of pHPT patients and should be routinely considered in preoperative planning.

Strong Recommendation - Moderate quality evidence

Pathogenesis

The etiology of pHPT may be sporadic or inherited. The vast majority of pHPT cases are sporadic. Acquired pHPT, a subset of sporadic disease, is associated with several types of environmental exposure.

Radiation Exposure

The evidence for an association between exposure to ionizing radiation and pHPT includes epidemiologic studies from nuclear disasters, studies on the medical use of external beam radiation, and case reports following radioactive iodine ablation. Among approximately 4,000 atomic bomb survivors of Hiroshima, pHPT was diagnosed in 19 people.¹⁰⁵ The prevalence increased with radiation dose, and younger people seemed to be more susceptible. Other epidemiological studies from Hiroshima also demonstrated an association between incidence of parathyroid tumor and distance to the epicenter.¹⁰⁶ Similarly, liquidators for the Chernobyl disaster had an increased risk of pHPT when compared to controls.¹⁰⁷ The first case report linking external beam radiation with pHPT was reported in 1975 in a woman who was treated for hirsutism.¹⁰⁸ Multiple reports have since suggested that therapeutic external radiation to the head and neck increases the risk

of pHPT. Consistent with what was observed following nuclear disasters, the relative risk is dose and age-dependent. The incidence of MGD with exposure to radiation is similar to pHPT overall, however there is a higher risk of metachronous and recurrent disease.¹⁰⁹

Lithium Exposure

Lithium carbonate, a mood stabilizer initially used for the treatment of psychiatric diseases in 1949, was first associated with pHPT in 1973.¹¹⁰ Lithium has been shown to stimulate parathyroid function and increase the risk of developing pHPT.¹¹¹ While the precise mechanism remains unclear, lithium-associated pHPT has been reported to occur in as many as 15% of chronic lithium users (defined as >10 years). In lithium-associated pHPT the rates of MGD have been reported to be as high as 83%.^{51-54,112} Lithium exposure increases the risk of both parathyroid adenoma and MGD.¹¹²

Genetic and Molecular Alterations

Various mutations and molecular alterations have been described in pHPT and affect the rate of MGD. The specific operative management of inherited forms of pHPT is addressed in Section 9.

- **MEN1** (Section 1) is a putative tumor suppressor gene associated with the MEN1 syndrome, of which pHPT is the most common manifestation with greater than 70% penetrance by age 50.¹¹³ The protein function and tumor suppressor mechanism of the MEN1 gene product is incompletely understood but appears to involve control of cell proliferation, apoptosis, and DNA repair through epigenetic regulation of histone modifications and chromatin structure.¹¹⁴ Patients with this syndrome harbor a mutated copy of the MEN1 gene, which produces the protein product menin, and the subsequent loss of heterozygosity typically results in MGD from independent clonal adenomas that clinically are termed nodular hyperplasia. The MEN1 gene is also frequently mutated in sporadic parathyroid adenomas.¹¹⁵ Although asymmetric size may be encountered during surgical exploration, hyperplasia of all parathyroid glands is the expected anatomic finding in patients with MEN-1 and the risk of persistent pHPT is higher when surgeons perform less than subtotal parathyroidectomy (Section 9).

62,116

- **RET** is a tyrosine kinase receptor and proto-oncogene that is heterogeneously mutated in MEN2A.¹¹⁷ Gain-of-function point mutations in the RET gene result in a variety of phenotypes. The penetrance of pHPT in MEN

2A is approximately 5- 20%, and varies by codon mutation.^{118,119} Asymmetric MGD is common.¹²⁰ Unlike MEN1 mutations, activating RET mutations are not found in sporadic pHPT. Due to the associated risk of medullary thyroid cancer, MEN2A patients with pHPT typically require total thyroidectomy and may require central neck dissection.¹²¹ Due to the heterogeneity of parathyroid gland size, only selective resection of enlarged glands is typically needed (Section 9).

- **PRAD1** is a proto-oncogene that encodes cyclin D1, a protein that regulates the cell cycle. Chromosome 11 rearrangement involving the PRAD1 gene result in the dysregulated expression of cyclin D1, which drives parathyroid cell proliferation, resulting in clonal expansion and adenoma formation.¹²² Cyclin D1 overexpression is common in sporadic adenomas but is not observed in sporadic hyperplastic glands.¹²³

- **CDC73** (formerly known as HRPT2) is a tumor suppressor gene associated with the HPT-JT, parathyroid cancer, and familial isolated hyperparathyroidism syndromes.³⁹ CDC73 encodes the parafibromin protein, which is a component in a complex that includes RNA polymerase II, which regulates transcriptional and post-transcriptional pathways. Germline and sporadic mutations in CDC73 can be found in parathyroid carcinoma.^{124,125}

- **RECOMMENDATION 2-2:** Exposure-related and genotype-phenotype correlations are predictive of parathyroid anatomy and pathology, and should be considered as they may impact the planning and conduct of surgery.

Strong Recommendation - Moderate quality evidence

3. INDICATIONS AND OUTCOMES OF INTERVENTION

Definitive Treatment of Symptomatic Patients

Parathyroidectomy is the only definitive therapy for pHPT. Observation and pharmacologic therapy are both less effective and less cost-effective than surgery, even when the patient is considered asymptomatic.¹²⁶

There is broad agreement among experts that the best treatment for patients with overt signs and symptoms of pHPT is parathyroidectomy.^{3,127-129} Parathyroidectomy is indicated for all willing surgical candidates with a

confirmed diagnosis of primary hyperparathyroidism who have overt signs or symptoms of pHPT. Because patients considered to be asymptomatic frequently report improvement in quality of life indices after curative parathyroidectomy referral to an experienced parathyroid surgeon who can discuss the risks and likely outcomes is advised.^{34,35,130,131}

- **RECOMMENDATION 3-1:** Parathyroidectomy is indicated, and is the preferred treatment, for all patients with symptomatic pHPT.

Strong Recommendation - High quality evidence

Further Indications for Parathyroidectomy

pHPT impacts multiple organ systems (Section 1). Some signs, symptoms and features may be objective and measurable, but some symptoms are subjective and difficult to quantify. The symptoms of pHPT are no less important to the patient when they are difficult to document. Even patients considered to be truly asymptomatic may benefit from referral to an experienced parathyroid surgeon who can discuss the risks, benefits, and likely outcomes of parathyroidectomy particularly since some patients who deny symptoms on presentation find that they feel better after surgery.

Total Serum Calcium Level

Parathyroidectomy is indicated when the total serum calcium is >1 mg/dl above the upper limit of normal range for the assay. Long-term hypercalcemia should be avoided because of the potential deleterious effects that include bone remodeling, vascular stiffness, nephrolithiasis and impaired renal function.^{128,132-145}

- **RECOMMENDATION 3-2:** Parathyroidectomy is indicated when the serum calcium level is > 1 mg/dl above normal, regardless of whether objective symptoms are present or absent.

Strong Recommendation - Low quality evidence

Classical Target Organ Manifestations--Renal

Parathyroidectomy is indicated when there is objective evidence of end-organ effects on the kidney.

The renal complications of pHPT include kidney stones, nephrocalcinosis, and decreased GFR and

concentrating capacity. Historically, the incidence of kidney stones in patients with pHPT was >50%¹⁴⁶, however contemporary series reveal that the incidence of clinically apparent stones has decreased to <20%.^{31,147,148} The prevalence of silent nephrolithiasis is not known. Clinically silent nephrolithiasis or nephrocalcinosis may be detected on renal imaging (Section 1). Following successful parathyroidectomy, the probability of developing new kidney stones decreases markedly - although a small risk remains likely due to coexisting idiopathic hypercalciuria.¹⁴⁹⁻¹⁵¹ Renal insufficiency and pre-existing nephrocalcinosis do not resolve, although surgery may prevent pHPT-related decline in GFR and clearly lessens the chance of new kidney stone formation. The continued impact of pHPT is halted by surgery.¹⁵²⁻¹⁵⁴ The development of a renal complication of pHPT is a strong indication for parathyroidectomy. Functional changes, particularly a decrease in GFR to < 60 ml/min, are also an indication for surgical intervention.^{56,149,151,155-158}

- **RECOMMENDATION 3-3:** Parathyroidectomy is indicated for objective evidence of renal involvement including silent nephrolithiasis on renal imaging, nephrocalcinosis, hypercalciuria > 400 mg/dL with increased stone risk, or impaired renal function (GFR < 60 cc/min).

Weak Recommendation -Low quality evidence

Classical Target Organ Manifestations--Skeletal

Parathyroidectomy is indicated when there is objective evidence of end-organ effects to the skeleton. pHPT causes a decline in BMD which is most pronounced at cortical bone sites on DXA, such as the distal third of the radius. Increased cortical porosity is evident on bone histomorphometry. Recent data obtained using higher level imaging, including high-resolution peripheral quantitative computed tomography and trabecular bone score (TBS) analysis of DXA lumbar spine images, have shown that even mild pHPT has negative effects on trabecular bone as well.

Parathyroidectomy improves BMD in both symptomatic and asymptomatic patients, and reverses the porosity of cortical bone and increases cancellous bone volume.^{128,159-161} In a cohort of patients with pHPT who underwent curative parathyroidectomy and who were observed for 15 years, there were uniform sustained

increases in BMD.^{128,162} The mean increase in BMD at the femoral neck was 14% at 10 years.¹²⁸ In comparison, the cohort of patients with untreated disease and followed for 15 years had declines in BMD at the femoral neck and distal radius of 10% and 35%, respectively.¹⁶² These long-term observational data extend our knowledge from prospective randomized controlled short-term studies of observation versus parathyroidectomy, where BMD was found to be improved in the surgical arm compared to the observation group.^{160,161} In a 24 month study, patients who underwent parathyroidectomy had improvements in BMD (measured by DXA) and bone quality (measured by TBS), whereas observed patients had no improvement in BMD and those with a history of fracture had further reductions in TBS.¹⁶³ Data on fracture incidence after surgery are less robust, and level one data are lacking. However, in several controlled cohort studies, a reduction in fracture rate has been seen in patients who underwent curative parathyroidectomy.^{132,164-166} Furthermore, this benefit does not appear to be limited to patients with just the most severe bone disease. In a retrospective cohort study the risk of fracture was decreased after parathyroidectomy in patients with normal, osteopenic, or osteoporotic bone.¹⁶⁶ Since parathyroidectomy improves bone mineral density and bone microarchitecture, all pHPT patients with a history of osteoporotic fracture (fragility fracture or vertebral compression fracture clinically or on vertebral imaging) or osteoporosis by BMD testing (defined as a T score ≤ -2.5 at any site) should undergo parathyroidectomy.^{138,162,165,167-174}

- **RECOMMENDATION 3-4:** Parathyroidectomy is indicated in patients with pHPT and osteoporosis, fragility fracture, or evidence of vertebral compression fracture on spine imaging.

Strong Recommendation - High quality evidence

Age 50 Years or Less at Diagnosis

Patients ≤ 50 years of age at the time of pHPT diagnosis will require prolonged monitoring, which is expensive; and even modest increases in calcium and/or PTH levels may impact long-term health, including potentially increasing the risk of cardiovascular, cerebrovascular, and renal disease. More importantly, younger patients have a markedly increased incidence of progressive disease over a decade of follow-up. Among those

≤50 years at pHPT diagnosis, two-thirds will have disease, while less than 25% of those >50 years will have disease progression during a decade of observation.^{140,175-180}

- **RECOMMENDATION 3-5:** Parathyroidectomy is indicated when pHPT is diagnosed at ≤ 50 years regardless of whether objective or subjective features are present or absent.

Strong Recommendation - Moderate quality evidence

Clinical or Biochemical Concern for Parathyroid Carcinoma

Parathyroid carcinoma (Section 12) is responsible for <1% of cases of pHPT.^{181,182} The diagnosis may be difficult to make preoperatively, but should be considered in patients with marked hypercalcemia (>14 mg/dL), evidence of local invasion, or a palpable parathyroid mass.¹⁸³ Patients with vocal cord paralysis, dyspnea, dysphagia, or other signs or symptoms that could be consistent with invasive disease should be managed surgically because parathyroidectomy is the only potentially curative treatment.^{184,185}

- **RECOMMENDATION 3-6:** Parathyroidectomy is indicated when the clinical or biochemical evidence is consistent with PCA.

Strong Recommendation - High quality evidence

Poor Patient Compliance or Inadequate Follow-Up

Patients who choose not to have surgery should be followed with annual biochemical evaluation and DXA every 1-2 years to assess for disease progression. If the patient does not have the means or desire to adhere to a planned observation schedule, or has indicated that he or she is unwilling to comply with adequate follow-up, parathyroidectomy should be offered.^{134,160,184-186}

- **RECOMMENDATION 3-7:** Parathyroidectomy is the preferred treatment for patients who are unable or unwilling to comply with observation protocols.

Strong Recommendation - Low quality evidence

Neuropsychiatric Symptoms

Neurocognitive and neuropsychiatric disturbances are frequent complaints of patients with pHPT, and may include easy fatigability, lassitude, depression, anxiety, irritability, cognitive impairment and disordered sleep.³³ Patients with pHPT, even those considered “asymptomatic”, report lower quality-of-life and more psychological symptoms than age- and sex-matched controls.¹⁶¹ A substantial body of literature indicates that, at baseline, patients with pHPT frequently suffer from neurocognitive and neuropsychiatric symptoms and that curative parathyroidectomy is associated with some degree of improvement in these symptoms.^{40,142,160,187-195} These improvements have been confirmed using recognized psychosocial assessment tools and clinical neuropsychiatric measures. Unfortunately, symptoms of pHPT overlap with those of many other common diseases, and may be hard to decipher for patients and their primary caregivers. Patients with pHPT may go unrecognized or undiagnosed if their neurocognitive symptoms are not correctly attributed to pHPT, or may have neuropsychiatric symptoms that are not solely attributable to pHPT. Both surgeons and patients should have realistic expectations about the potential benefits of surgery.^{38,189,192,196-201}

A prospective controlled study of patient-reported symptom improvement following parathyroidectomy using the *Parathyroidectomy Assessment of Symptoms* (PAS) tool revealed that most patients have a significant improvement in symptoms within 10 days of surgery, and that at one year they report a 60% improvement in their overall health status.¹⁸⁸ A follow-up of the same cohort 10 years postoperatively revealed sustained improvements in PAS score compared to baseline. These data indicate that the symptom improvement was significant and durable.¹⁹⁴ In another prospective survey study, most patients reported that fatigue and musculoskeletal pain improved within the first week, but that peak improvement for most symptoms occurred at 6 weeks after surgery.²⁰² In a study using both the Short Form Health Survey (SF-36) and PAS tools, patients who underwent parathyroidectomy had a rapid, durable, and significant improvement in PAS score and all SF-36 domains except for social functioning.¹⁹² In 212 patients who underwent curative parathyroidectomy, pronounced improvement was found in depressive and anxiety symptoms, and visuospatial and verbal memory at 1, 3 and 6 months. Interestingly, these improvements correlated with the extent of reduction in PTH.^{40,130}

The highest quality data in this area come from 3 randomized controlled trials of surgery vs. observation using the SF-36 tool. In one, preoperative patients were found to have significant impairment in 5 of 8 domains compared to normative data, and after surgery, had significant improvement in 7 of 8 domains.¹⁸⁹ In another study, parathyroidectomy led to a significant improvement in quality of life in the SF-36 domains of bodily pain, general health, vitality, and mental health.¹⁶⁰ In a third study, patients randomized to surgery demonstrated improvements in social and emotional role functioning as measured by SF-36 and lower anxiety and phobia scores.¹⁴² Although there was a benefit to surgery in each trial, these data do not allow the treating physician to assure a given patient about the expected response to parathyroidectomy, as there were inconsistent results regarding the degree and domains of improvement in neurocognitive function across the 3 trials. Overall, a substantial body of literature demonstrates that patients with pHPT frequently suffer from neurocognitive and neuropsychiatric symptoms, and that curative parathyroidectomy is associated with some degree of improvement in these symptoms.

- **RECOMMENDATION 3-8:** Parathyroidectomy is recommended for patients with neurocognitive and/or neuropsychiatric symptoms that are attributable to pHPT.

Strong Recommendation - Low quality evidence

Cardiovascular Manifestations

Patients with untreated pHPT may have more severe cardiovascular disease and poorer survival. There is a strong association between cardiovascular disease and marked hypercalcemia. An increased incidence of myocardial infarction, hypertension, stroke, congestive heart failure, and diabetes has been observed in pHPT patients.²⁰³ Diastolic dysfunction and left ventricular hypertrophy (LVH) are more common in pHPT,²⁰⁴⁻²⁰⁷ and LVH appears to be related to PTH levels and may improve after parathyroidectomy.^{204,206} Parathyroidectomy has been associated with improvement in left ventricular diastolic function, cardiac irritability, and a reduction in exercise-induced ST segment depression which was maintained 5 years after surgical cure.²⁰⁸ In a prospective case-controlled study of patients with symptomatic pHPT, left ventricular mass, systolic and diastolic function,

and smooth muscle-mediated vasodilatation were abnormal at baseline and were each improved 6 months after curative parathyroidectomy.²⁰⁹

Some studies have shown a higher risk of cardiovascular disease and death in patients with untreated pHPT. A Danish cohort study found a higher mortality rate due to stroke and cancer.²¹⁰ Hypertensive Swedish patients with pHPT were found to have a 50% higher mortality than normotensive patients, and there was a decline in mortality after parathyroidectomy that was significantly better in the hypertensive group.²¹¹ Other Scandinavian studies have also found an increased cardiovascular mortality.²¹²⁻²¹⁶ In one study there was also an increased risk of myocardial events up to 10 years before surgery, and it decreased to almost baseline 1 year after parathyroidectomy.²⁰³ In a retrospective observational study of 1,683 patients from Scotland, patients with untreated pHPT were found to have increased rates of all-cause and cardiovascular mortality.⁷⁷ There was also an increased risk of renal dysfunction and fractures. In a follow-up study, elevated PTH at presentation was found to be the only significant predictor of long-term survival and cardiovascular outcomes in untreated pHPT.²¹⁷

In contrast to the literature on classical severe pHPT, data on mild pHPT are less clear regarding cardiovascular outcomes. The only longitudinal study conducted in patients with mild pHPT found that overall survival was not affected, and indeed the relative risk of cardiovascular mortality was decreased (RR 0.6). Patients with the highest serum calcium levels, however, did have an increased risk of death.²¹⁸ Recent observational studies in mildly affected patients (mean serum calcium 10.5 mg/dl) did not demonstrate left ventricular hypertrophy, diastolic dysfunction or increased frequency of valvular calcification, although carotid stiffness and intima medial thickness was increased.²¹⁹⁻²²¹ None of these findings improved after parathyroidectomy.²²²

Although some studies^{205,223,224} have suggested an improvement in hypertension after parathyroidectomy, most indicate that hypertension is not reversible with surgical cure of pHPT.^{225,226} There are now clear data from randomized controlled trials demonstrating this lack of hypertensive response. As such, patients should not be operated on solely for improvement of hypertension.

Further study is required to determine if early parathyroidectomy can mitigate the cardiovascular morbidities of pHPT. Although some experts contend that parathyroidectomy should not be performed specifically to improve cardiovascular endpoints in otherwise asymptomatic patients³, it is prudent to weigh these data and the possibility of mitigating cardiovascular morbidity and mortality on a case-by-case basis.

- **RECOMMENDATION 3-9:** Parathyroidectomy may be offered to surgical candidates with cardiovascular disease who might benefit from mitigation of potential cardiovascular sequelae other than hypertension.

Weak Recommendation - Low quality evidence

Patients with Other Non-Traditional Symptoms

Observational studies in small cohorts have demonstrated a variety of non-traditional symptoms that appear to be improved following successful parathyroidectomy. These include but are not limited to: muscle strength^{227,228}, functional capacity³⁵, digestive symptoms^{132,229-234}, sleep patterns^{41,195,196}, and fibromyalgia symptoms.²³⁵ Unfortunately, most of the data are from studies with small cohorts and short-term follow-up. Additional investigation, ideally prospective studies with larger cohorts and long-term follow-up, is needed to further understand these symptoms and how best to counsel patients regarding expectations following parathyroidectomy. However, many patients with non-traditional symptoms will have other indications for surgery such as skeletal, renal, or neurocognitive manifestations, and these symptoms should be the focus of preoperative discussion concerning risk and benefit.

- **RECOMMENDATION 3-10a:** The non-traditional symptoms of muscle weakness, functional capacity and abnormal sleep patterns should be considered in the decision for parathyroidectomy

Weak Recommendation - Moderate quality evidence

- **RECOMMENDATION 3-10b:** The non-traditional features of reflux and fibromyalgia symptoms may be considered in the decision for parathyroidectomy.

Insufficient

Relationship of Surgical Volume to Outcomes

For experienced parathyroid surgeons, the expected cure rate of an index operation for sporadic pHPT is >95%²³⁶⁻²⁴¹ (Sections 7 & 8) and for reoperation is >90%²⁴²⁻²⁴⁹ (Section 17). Historically, the success rate for surgeons who performed <10 parathyroidectomies per year was considerably lower, at approximately 70%.²⁵⁰ More recent observational studies have documented that when cervical endocrine procedures are performed by less experienced surgeons, surgeon volumes inversely correlate with complications, cost, and length of stay.^{251,252} Low hospital parathyroidectomy volume has also been correlated with higher complications, failed surgery, and the need for subsequent reoperation.²⁵²⁻²⁵⁵ In a survey study, self-reported complication rates of surgeons who perform 1-5 parathyroid operations per year were approximately double those reported by surgeons who perform >50 operations per year.²⁵⁶

- **RECOMMENDATION 3-11:** Parathyroidectomy should be conducted by surgeons with adequate training and experience in pHPT management.

Strong Recommendation - Moderate quality evidence

Outcomes of Observation and/or Pharmacologic Management

In clinical practice, patients who are not safe surgical candidates must be managed medically, and some patients with asymptomatic pHPT are more likely to be monitored, or treated pharmacologically, than referred for surgery.^{55,76,257} While many pharmacologic agents have been used in an attempt to either reduce the serum calcium or stabilize BMD, none have improved both. Unlike surgery, which improves both serum calcium and BMD, long-term data on the use of pharmacologic agents are lacking. Bisphosphonates such as alendronate have been used to treat low BMD with modest effect, but there are no data on fracture.²⁵⁸⁻²⁶⁰ Cinacalcet is effective at modestly lowering serum calcium levels and is FDA-approved for severe hypercalcemia in patients who are unable to undergo parathyroidectomy. There does not, however, appear to be a benefit of cinacalcet on BMD or renal effects in patients with pHPT.²⁶¹

In a formal cost-effectiveness analysis of observation versus cinacalcet vs. surgery for asymptomatic pHPT, observation was found to be less costly, but also less effective than surgery.¹²⁶ In another formal cost-effectiveness analysis parathyroidectomy was found to be the most cost-effective strategy for patients with at least 5 years of remaining healthy life, whereas observation was the optimal strategy at all shorter life expectancies. Pharmacologic treatment was not optimal at any life expectancy.²⁶²

Despite these data, contemporary and historical utilization studies suggest that only approximately 20-30% of patients with pHPT in the United States are treated surgically.^{55,76,257,263} One study found that at a larger tertiary care referral center, only one-third of outpatients with hypercalcemia had a PTH measured.²⁶³ Data from a robust integrated health care delivery system in California found that elderly patients appear to have the greatest delay in diagnosis and are the least likely to undergo parathyroidectomy, even though the prevalence of pHPT is highest in this population⁷⁶ and the results in geriatric patients are excellent.^{35,264}

Undiagnosed and untreated patients with pHPT have an increased risk of fracture.^{164,265} Osteoporotic fracture in elderly patients may lead to hospitalization, reduction in functional capacity, or even loss of independence, each of which must certainly encumber the patient and society economically, and also diminish quality of life. For those patients treated surgically, there is a sustained postoperative rise in BMD^{128,162} and a reduced risk of fracture.^{132,164,165,265} The cost-savings of fracture avoidance in this population has not been studied. As discussed above, improvements can also be anticipated in many neurocognitive and renal manifestations of disease, which should have additional impacts on cost and quality of life. The cost-savings of avoiding these complications is also unknown. Well-designed prospective studies are required In order to determine the true burden of untreated disease, and the costs and outcomes of surgical, pharmacologic, and observation strategies.

Between 1990 and 2014, 4 workshops have been convened to develop and revise guidelines for the treatment of patients with pHPT who are considered asymptomatic. New, more rigorous observation protocols have been recommended in the 4th International Workshop Guidelines published in 2014.³ The costs and cost-effectiveness of these new protocols has not yet been examined.

In summary, there is no effective pharmacologic equivalent to surgery, and the most effective treatment for pHPT is surgery, even in those patients considered to be asymptomatic. Long-term pharmacologic therapy or observation are, respectively, more costly and less effective than parathyroidectomy.

- **RECOMMENDATION 3-12:** Operative management is more effective and cost-effective than either long-term observation or pharmacologic therapy.

Strong Recommendation – Moderate quality evidence

Nonoperative Management

Parathyroidectomy for pHPT is not recommended when the risks of surgery or anesthesia are outweighed by the anticipated benefits of cure and/or when the outcome is likely deleterious, as with severe or over-riding medical illness. In patients who meet none of the above indications for surgical intervention, refuse surgery, or are considered prohibitively high risk, medical intervention should be employed aimed at mitigating specific sequelae. Many patients with mild disease will progress over time.¹⁶² Other situations that may prompt nonsurgical management include first trimester pregnancy, severely limited cervical access, prior vocal cord paralysis, and a short expected lifespan.

4: PARATHYROID LOCALIZATION MODALITIES: What Imaging to Perform and When

In the often-quoted words of Dr. John Doppman, who for many years led the endocrine radiology program at the National Institutes of Health, “the only localization study indicated in a patient with untreated primary hyperparathyroidism is the localization of an experienced endocrine surgeon”.²⁶⁶ Over time, however, the number and quality of parathyroid imaging modalities has proliferated, as have the number of studies investigating their utility. There are no widely agreed upon definitions of a true positive or true negative imaging result, and no consensus as to whether a true positive is considered localization to the exact gland, the quadrant of the neck, or the correct side (which is termed lateralization). For these reasons, and also given the wide variation in the quality of imaging from institution to institution, one can only assess sensitivity,

specificity, negative predictive value, and positive predictive value in general terms. The standard parathyroid imaging modalities include ultrasound (US), sestamibi scanning, and more recently 4-dimensional computed tomography (4D-CT).

Guiding Principles of Parathyroid Imaging

1. For any patient, the diagnosis of pHPT is biochemical (Section 1). Imaging has no demonstrated utility in confirming or excluding the diagnosis.
2. The decision to operate is not based on imaging findings and imaging results should not be used to select patients for surgical referral. Patients with negative imaging remain candidates for parathyroidectomy given the high rate of false negative imaging, especially in cases of MGD.²⁶⁷⁻²⁷⁰
3. A number of studies have reported that when patients with negative results have imaging repeated at high-volume centers, the sensitivity of localization improves to as high as 92%.²⁷¹⁻²⁷⁴ There is a great deal of regional variability in imaging accuracy.²⁷⁵
4. Imaging is obtained after deciding to proceed with parathyroidectomy, and is performed for the purpose of operative planning.
5. As will be discussed in individual sections on specific modalities below, parathyroid imaging is significantly less accurate in the setting of MGD.^{47,236,267-269,271,272,275-277}

Patients with pHPT who are candidates for surgery should be referred to an expert clinician so that he/she may decide which imaging studies to perform. Experienced providers know the local expertise, costs, alternatives, indications, and quality of available imaging modalities and are in the best position to decide which test(s) to perform. In addition, experienced providers often practice in facilities where parathyroid imaging has been refined to a greater degree of accuracy.

Surgeons should personally review the pertinent imaging studies.²⁷⁵ Recommendations regarding parathyroid imaging in the reoperative setting appear in Section 17.

- **RECOMMENDATION 4-1:** Patients who are candidates for parathyroidectomy should be referred to an expert clinician to decide which imaging studies to perform based on their knowledge of regional imaging capabilities.

Strong Recommendation - Low quality evidence

- **RECOMMENDATION 4-2:** Patients who are candidates for surgery and have negative or discordant imaging should still be referred to a parathyroid surgeon for evaluation.

Strong Recommendation - Low quality evidence

Standard Imaging Modalities

Ultrasound (US)

Cervical US is performed with a high-frequency probe. The central and lateral neck compartments should be imaged. The benefits of US include lack of ionizing radiation, low cost, wide availability, and ease of use in the office setting. Perhaps the greatest strength of US is the ability to assess for concomitant thyroid disease. Since thyroid disease occurs in 30 to 51% of patients with pHPT, adequate preoperative evaluation of the thyroid is critical (Section 11).^{278,279}

The utility of US is limited by high body mass index, variability in the physical characteristics of diseased glands (echogenicity, vascularity, etc.), false positives from thyroid pathology, ultrasonographer experience and poorer performance with MGD and posterior gland locations.²⁷⁵ Low-lying superior glands, especially those in the retroesophageal/retrotracheal positions, may not be visible due to their depth and impeded sound transmission through gas-containing structures like the esophagus or trachea. Similarly, inferior parathyroid glands low in the thyrothymic ligament and mediastinum may be obscured by overlying bone. Normal parathyroid glands are typically not visible due to their small size (2-3 mm).

Numerous studies have demonstrated that performance of US by a dedicated parathyroid/thyroid sonographer improves the accuracy of parathyroid localization.²⁸⁰⁻²⁸⁶ The specialty of the dedicated sonographer

matters less than their familiarity with cervical anatomy, normal and ectopic locations, and the physical characteristics (shape, vascularity, and echogenicity) of normal and abnormal parathyroids.

In combination with intraoperative parathyroid hormone monitoring, US by a dedicated parathyroid sonographer can be used successfully as the only localization study when a clear parathyroid adenoma is identified.^{281-285,287} Meta-analyses have demonstrated a sensitivity of 76% (95% confidence interval [CI] 70-81%) to 79% (95% CI 77-80%) while single institution series have reported sensitivity as high as 82%.^{275,280,282,283,286-288} However, the sensitivity drops considerably to 35% (95% CI 30-40%) in the setting of MGD.²⁷⁵ The specificity of US has been reported to be as high as 96% in some single institution series.^{286,289} A recent meta-analysis found a pooled positive predictive value of 93.2% (85-100%).²⁸⁸ A few studies have demonstrated that US by an experienced parathyroid sonographer is the least costly imaging modality and that combining it with another form of imaging, such as sestamibi or 4D CT, is the most cost-effective strategy.^{272,277,290}

- **RECOMMENDATION 4-3:** Cervical US is recommended to localize parathyroid disease and assess for concomitant thyroid pathology.

Strong Recommendation - Low quality evidence

Parathyroid Fine Needle Aspiration Biopsy (FNAB) with PTH Washout

FNAB of parathyroid lesions is highly specific, with some groups demonstrating 100% specificity and no false positives.²⁹¹⁻²⁹⁴ However, FNAB can be associated with a number of undesirable results. Cytologically, parathyroid tissue may mimic follicular thyroid lesions and therefore, specific washout of the needle for concomitant PTH measurement is highly desirable if FNAB is performed. In addition, parathyroid FNAB cannot reliably distinguish between benign and malignant parathyroid disease and can also lead to seeding or dissemination of parathyroid tissue, either malignant or benign (parathyromatosis). Although small series have found no cases of seeding, the theoretical risk likely exceeds any diagnostic value.^{291,292} Parathyroid FNAB may also cause sequelae that make subsequent surgery more difficult (hematoma, abscess, inflammation), and can also create histologic artifacts that mimic parathyroid cancer on final pathology (Section 12).²⁹⁵ For these

reasons, the committee reached strong consensus that parathyroid FNAB should be reserved for difficult cases of localization such as intrathyroidal parathyroids and reoperative cases.²⁹³

In addition, parathyroid FNAB should not be performed when the diagnosis of parathyroid cancer is suspected preoperatively, due to all of the aforementioned reasons as well as the fact that FNAB cannot reliably distinguish between benign and malignant parathyroid lesions (Recommendation 12-4).

- **RECOMMENDATION 4-4:** Preoperative parathyroid FNAB is not recommended except in unusual, difficult cases of pHPT and should not be performed if parathyroid cancer is suspected.

Insufficient

Radioisotope Scintigraphy (Sestamibi)

^{99m}-technetium sestamibi has become the dominant radioisotope used in parathyroid scintigraphy. Sestamibi imaging depends on the differential uptake and retention of radiotracer in mitochondria-rich cells. There are a number of different sestamibi protocols employed including dual phase, I¹³¹ subtraction, single photon emission CT (SPECT), and SPECT-CT imaging. Each protocol has individual strengths and weaknesses. For example, SPECT imaging provides 3-dimensional information that helps give better anatomic detail. The technique is especially helpful in identifying posteriorly located low-lying superior adenomas that are typically obscured by thyroid uptake. This modality can be performed with an attenuated CT component to reduce radiation exposure.^{269,296} In addition to significant differences in institutional expertise, this multiplicity of protocols further contributes to the wide variability of reported results in the literature.

The main benefits of sestamibi imaging include the ability to assess for deep cervical and ectopic glands (including in the mediastinum), a relatively low exposure to ionizing radiation, and ability to assess for function of autotransplanted tissue to the forearm or elsewhere. The utility of sestamibi is limited by its inability to assess the thyroid, potential false positives from thyroid nodules, and poor performance in MGD.²⁶⁹ One meta-analysis found that in the setting of 4 gland hyperplasia and double adenoma, the sensitivity decreased to 44% (95% CI 41-48%) and 33% (95% CI 2-62%), respectively.²⁷⁵ Highlighting the problem of limited resolution

with sestamibi, several studies have shown that the sensitivity is strongly correlated with gland weight such that the sensitivity for glands >500mg in size is 93%, whereas for those <500mg the sensitivity is only 51%.²⁹⁷

The sensitivity and specificity of sestamibi imaging varies widely in the literature due to regional variations in expertise with various protocols employed.²⁹⁸⁻³⁰⁰ In one meta-analysis, the pooled sensitivity and positive predictive value for Sestamibi-SPECT was found to be 79% (49-91%) and 91% (84%-96%), respectively.²⁷⁵ However, the range of sensitivity varies from as low as 45% to as high as 92% in single institution studies.^{301,302} In another meta-analysis, the authors found a similarly low pooled sensitivity of 72% with a wide range of reported results (39-92%).³⁰¹

- **RECOMMENDATION 4-5:** An experienced clinician should help determine which type of imaging to use, based on knowledge of their region's imaging capabilities.

Strong Recommendation - Moderate quality evidence

Combined US and Sestamibi

Combined US and sestamibi imaging increases the accuracy of parathyroid localization compared to either technique alone, improving sensitivity significantly.^{285,303-305} In a prospective trial looking at operative success using different imaging modalities, combining the 2 techniques predicted a higher surgical success than utilizing either modality in isolation.²⁵³ However, combining both modalities still has limited success in identifying MGD with only a 30-60% rate of correctly identifying the condition.^{306,307}

Four-dimensional Computed Tomography (4D-CT)

While traditional CT imaging has very limited utility in parathyroid disease, the 4D-CT protocol has emerged as an excellent modality. The 4th dimension in 4D-CT refers to the differential pattern of contrast enhancement in parathyroid tissue over time. Typically, parathyroid adenomas demonstrate rapid uptake and washout of contrast compared to thyroid and adjacent tissue. Most 4D-CT protocols utilize multiple thin-cut passes with a resolution of 1mm or better.

The main benefit of 4D-CT is that it provides both precise anatomic detail as well as functional data from the contrast enhancement patterns for both typically and ectopically located glands.^{272,273,276,308} In

addition, 4D-CT is perhaps the only imaging modality that can reliably identify normal parathyroid glands, and some groups have advocated its use primarily in patients with mild hypercalcemia who have a higher likelihood of smaller adenomas or MGD.^{271,272,276} Some series have found sensitivities for MGD ranging from 62.5-85.7%.^{272,276} In addition, 4D-CT is effective in reoperative parathyroid surgery.³⁰⁸ The main disadvantages of 4D-CT are cost, significantly increased radiation exposure (which is of special concern in younger patients), lack of wide availability, and requirement for a dedicated expert to interpret results.^{309,310} In an effort to reduce radiation exposure, a number of groups have found that limiting the number of phases captured during imaging had equivalent results to the more traditional 4-D CT imaging.^{311,312}

A number of centers have reported superior sensitivity and positive predictive value of 4D-CT in comparison to combined US and sestamibi. In one meta-analysis, 4D-CT had a sensitivity of 89% and positive predictive value of 93.5%.²⁸⁸ In direct comparison, 4D-CT had a greater sensitivity (88%) than US (57%) and sestamibi (65%).²⁷⁴ 4D-CT was also able to better predict the appropriate quadrant of the neck (70%) vs. only 30% with sestamibi.²⁷⁴ In one retrospective study, the accuracy of 4D-CT for laterality was 93.7% with 86.6% accuracy for localization to a specific quadrant.²⁷⁴ 4D-CT has a high sensitivity and specificity for lateralizing (85% and 94%) and predicting the exact location of diseased glands (66% and 89%) in patients with previously negative sestamibi scans.²⁷¹ US, sestamibi imaging, and 4D CT may be used preoperatively in pHPT independently or in combination, at the surgeon's discretion.

Magnetic Resonance Imaging (MRI) and other Non-Standard Modalities

Although MRI of the neck and chest for parathyroid localization is non-invasive and does not expose patients to ionizing radiation, this test is seldom used as a primary means of localization due to its relatively poor sensitivity and specificity and cost. Single institution series report sensitivities ranging from 43-71%.^{313,314} MRI is typically reserved for cases of difficult localization, such as re-operative parathyroid surgery or for patients who cannot be exposed to ionizing radiation, such as pregnant patients.³¹⁵⁻³¹⁷

Other image-guided modalities such as selective venous sampling and preoperative bilateral jugular vein sampling may provide additional data, but are generally not considered cost-effective in operative planning for

initial surgery^{291-293,316,318,319} and like MRI should not be used routinely. These examinations may be considered in cases of difficult localization or reoperation (Section 17).

- **RECOMMENDATION 4-6:** MRI and venous sampling can be considered in cases of reoperation, difficult localization, or when ionizing radiation is contraindicated.

Weak Recommendation - Low quality evidence

5. PREOPERATIVE MANAGEMENT

In addition to the standard preoperative management of patients undergoing surgery (risks of anesthesia, perioperative adjustment of anticoagulant medications, DVT prophylaxis, possible need for antibiotic prophylaxis, etc.), the preoperative management of patients undergoing parathyroidectomy should include care of significant hypercalcemia, evaluation of possible need for calcium and vitamin D supplementation, and evaluation of vocal cord function.

Calcium Supplementation/Restriction

The Food and Nutrition Board at the Institute of Medicine recommends an intake of 1000-1200 mg of calcium daily (between diet and supplements) for adults >18 years, although pHPT patients are often erroneously advised to restrict their calcium intake.³²⁰ Low dietary calcium intake has been shown to stimulate PTH secretion, which in turn acts to increase 1, 25-dihydroxyvitamin D synthesis (enhancing intestinal absorption of calcium) and worsen bone demineralization.³²¹⁻³²³

To clarify the effect of calcium intake on the biochemical parameters of pHPT, a longitudinal natural history study examined daily calcium intake thresholds of >300 mg, 300-800 mg, and >800 mg and found no effect on serum calcium, PTH, 25-OH vitamin D, 1, 25-OH vitamin D levels or urinary calcium excretion, although patients with elevated 1, 25-OH vitamin D levels had higher urinary calcium levels. The authors advocated normal calcium intake for pHPT patients with normal 1,25-OH vitamin D levels.³²⁴ In another study, asymptomatic pHPT patients with a daily calcium intake <450 mg were given a daily 500 mg supplement and had no significant increase in serum calcium level after 4 and 12 weeks, a decrease in serum PTH after 4 weeks, and a significant increase in BMD at the femoral neck after 52 weeks. These results suggest that pHPT patients

with low calcium intake might benefit from calcium supplementation to recommended levels,³²⁵ which was also recommended by the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism.³²² There are no data to support dietary restriction of calcium.

- **RECOMMENDATION 5-1:** Most patients with pHPT should follow Institute of Medicine guidelines for calcium intake.

Strong Recommendation -Moderate quality evidence

Vitamin D Supplementation

Vitamin D deficiency is common in patients with pHPT, and is commonly defined as 25-OH vitamin D levels <20 ng/mL while levels >30 ng/mL are considered sufficient.³²⁶ Current recommendations from the Institute of Medicine for adequate daily intake of vitamin D are 600–800 IU for adults, although there is consensus that in most of the US, approximately 800–1000 IU per day is required.³²⁶ In the past, patients with pHPT and vitamin D deficiency have sometimes been advised to refrain from vitamin D supplementation due to fears of exacerbating hypercalcemia and manifestations of pHPT. Although hypercalcemia can worsen occasionally, recent studies demonstrate that preoperative vitamin D repletion is safe and does not increase serum calcium levels.³²⁷⁻³³¹ The Fourth International Workshop on Asymptomatic Primary Hyperparathyroidism recommended preoperative supplementation to ≥ 20 ng/mL (50 nmol/L).³²²

In a meta-analysis and literature review of 10 studies (340 patients), preoperative vitamin D repletion in patients with pHPT and vitamin D deficiency produced no significant change in serum calcium levels despite a significant increase in 25-OH vitamin D levels;³³¹ although 5 patients developed hypercalcemia, requiring cessation of vitamin D, no patient developed hypercalcemic crisis. There also was a significant reduction in serum PTH levels with vitamin D replacement.³³¹ In a recent randomized placebo controlled trial, patients with pHPT and vitamin D insufficiency (defined in the study as <80 nmol/L; 32 ng/mL) were treated with 2800 IU daily cholecalciferol (D3) or placebo for 6 months prior to parathyroidectomy and for 6 months after cure.³³⁰ In the group randomized to cholecalciferol, 25-OH vitamin D increased from 50.2 to 94.2 nmol/L (20.1 to 37.7 ng/mL) and PTH levels decreased by 17% (p=0.01) during the first 25 weeks of treatment. Despite this, there

was no difference in any time point in serum or urinary calcium levels between the 2 groups, again suggesting that vitamin D replacement did not significantly increase serum calcium levels.

Although there are no specific regimens that are recommended for repletion of vitamin D in pHPT patients with preoperative vitamin D deficiency, some parathyroid surgeons today replete vitamin D preoperatively to reduce temporary postoperative paresthesias (Section 14). Since urinary calcium excretion will increase before vitamin D effects are reflected in rising serum calcium, vitamin D should be supplemented carefully in patients with hypercalciuria. In one study, marked hypercalciuria (urinary calcium >400 mg/d) occurred in some patients supplemented with a 50,000 IU dose of vitamin D.³²⁷

- **RECOMMENDATION 5-2:** Prior to parathyroidectomy, patients with pHPT who are vitamin D deficient can safely begin vitamin D supplementation.

Weak Recommendation –Low quality evidence

Preoperative Voice Evaluation

In patients undergoing parathyroidectomy, postoperative voice changes secondary to injury to the recurrent laryngeal nerve (RLN) or external branch of the superior laryngeal nerve (EBSLN) are uncommon, but are among the most anxiety-provoking complications.^{332,333} Although the reported incidence of hoarseness is as high as 10%, most postoperative voice changes are transient and secondary to laryngeal irritation, edema, or injury from airway management.^{334,335} The incidence of permanent vocal cord paralysis is estimated to be <1% after thyroid or parathyroid surgery.^{40,336,337} However, much of the literature regarding postoperative voice outcomes relates to thyroid surgery since more extensive dissection is generally required. Therefore, estimates of nerve injury during parathyroidectomy are likely to be the same, if not lower, than for thyroidectomy.

Voice evaluation is an essential component of the preoperative history and physical examination. In addition to carefully assessing voice quality, the surgeon should ask patients and family members about subjective voice changes, including persistent hoarseness.^{335,338} Preoperative voice problems may be unrelated since it is rare that the RLN is impinged upon or invaded by an abnormal parathyroid gland. If there are no voice changes, most patients do not require further examination of vocal cord mobility.³³⁸ Additional

preoperative evaluation is recommended for patients with subjective changes in voice quality, surgeon-documented voice abnormalities, or any history of prior surgery in which the vagus nerve or RLN was at risk for injury including previous thyroidectomy, parathyroidectomy, carotid endarterectomy, tracheostomy, cervical spine procedures, and thoracic procedures.^{335,338,339}

There are several modalities for laryngeal examination in the office setting. The method chosen should take into consideration the degree of clinical suspicion, costs, efficacy, and ease of performance. A non-invasive method is use of a directed light, head mirror, and laryngeal mirror, to directly visualize vocal fold mobility, although subtle alterations may be difficult to assess. Flexible laryngoscopy allows for evaluation of motion during speech and directed tasks (e.g., pronouncing ‘eee’, deep inspiration, or cough), and is a better tool to evaluate subtle changes in vocal fold motion. Videostrobolaryngoscopy provides detailed data on vocal fold pliability and symmetry, but is invasive and rather costly.³³⁵ Use of transcutaneous laryngeal ultrasonography has recently been described as a highly sensitive, operator-dependent, useful modality for evaluation of vocal cord mobility.^{340,341}

- **RECOMMENDATION 5-3:** Preoperative voice evaluation should include specific inquiry about subjective voice changes, with additional evaluation for significant voice changes or a history of prior at-risk surgery.

Strong Recommendation – Low quality evidence

Management of Severe Hypercalcemia

Severe hypercalcemia is rare in patients with pHPT. An acute increase in serum calcium level, referred to as hypercalcemic crisis, acute hyperparathyroidism, parathyroid storm, or (hyper)parathyroid crisis, typically occurs in patients with mild pHPT in the setting of severe or catastrophic intercurrent illness.^{342,343}

Hypercalcemic crisis should be considered with an albumin-corrected serum calcium >14 mg/dL and signs or symptoms of multiorgan dysfunction,^{342,344-346} including gastrointestinal (anorexia, nausea, vomiting, abdominal pain, pancreatitis), renal (dehydration, oliguria, acute kidney injury and acute nephrolithiasis),

cardiovascular (shortened QT interval), and neurologic symptoms (muscle weakness, confusion, lethargy, coma); patients with chronic severe hypercalcemia may report less significant symptoms.³⁴²⁻³⁴⁸

Patients with chronic severe hypercalcemia may be managed expectantly, although hospital admission should be considered for acute changes, particularly in mental status. The timely treatment of patients with hypercalcemic crisis is critical, as the condition is associated with a high rate of mortality.^{342,345} The goals of medical treatment include correction of the hypovolemic state, promotion of renal calcium excretion, and inhibition of accelerated bone resorption. In patients with a precipitating intercurrent illness, the underlying problem must be identified and treated. Initial management should be intravenous administration of isotonic saline, based on the degree of hypovolemia and the comorbidities; one approach suggests 3-4 L of normal saline for 24 hours, followed by 2-3 L per 24 hours, until adequate urine output is established.³⁴² Once the hypovolemia has been corrected, loop diuretics such as furosemide are utilized to block calcium reabsorption and promote calciuresis. Thiazide diuretics enhance calcium reabsorption and are contraindicated in the management of severe hypercalcemia. Restoration of euvolemia does not treat the underlying pathophysiology of the hypercalcemic crisis, which is excessive mobilization of calcium from bone. The use of intravenous bisphosphonates can be effective in lowering serum calcium levels, but is slow in onset and is not approved by the FDA for use in non-cancer hypercalcemia.^{342,348} Other agents include calcitonin and glucocorticoids. The effect of calcitonin is relatively short-lived and is most effective in combination with bisphosphonates.^{342,348}

Cinacalcet is an oral calcimimetic agent that activates the calcium-sensing receptor on parathyroid cells, increasing sensitivity to extracellular calcium to lower PTH and serum calcium levels. Cinacalcet has been shown to reduce and even normalize serum calcium levels in patients with pHPT, who may maintain normocalcemia over a prolonged period of time.^{162,349-351} However, cinacalcet has not been studied in patients with parathyroid crisis. It should be noted that in order to reduce calcium significantly, markedly higher doses (up to 90 mg twice daily) than the 30 mg twice daily currently FDA-approved for patients with pHPT may be required.¹⁶²

In patients with pHPT and severe hypercalcemia, medical management should be seen as a 'bridge' to expeditious parathyroidectomy for definitive management.³⁴²⁻³⁴⁸ The optimal timing for urgent

parathyroidectomy and stopping calcitonin and cinacalcet remains debated.^{284,344,347} Based on imaging results, MIP is an appropriate surgical approach for many patients (Section 7) although reported rates of parathyroid carcinoma are higher with severe hypercalcemia (4.5–12%), thus more extensive surgery may be required (Section 12).^{344,346,347}

- **RECOMMENDATION 5-4:** Patients with pHPT who present with hypercalcemic crisis should be medically managed, followed by parathyroidectomy.

Strong Recommendation – Low quality evidence

6. INTRAOPERATIVE PTH MONITORING (IPM)

Rationale

The use of intraoperative PTH monitoring (IPM) has its origins in the late 1980's at a time when bilateral neck exploration (BE) was the preferred operative approach and the use of preoperative imaging was not routine.³⁵² In 1991 the use of IPM was reported to predict postoperative normocalcemia in patients with pHPT.³⁵³ Intraoperative assays for rapid PTH measurement became commercially available in 1996, and today most endocrine surgeons consider IPM essential in helping to determine that all hyperfunctioning parathyroid tissue has been removed prior to leaving the operating room.^{93,98} Compared to BE which relies on comparative assessment of parathyroid gland size, IPM relies predominately on real-time assessment of gland function. IPM has exerted its greatest impact in focused operations when the surgeon removes an image-identified abnormal gland without dissecting and evaluating the other parathyroid glands. For initial image-guided surgery, positive imaging directs where to start exploration and the results of intraoperative PTH monitoring help to terminate it.

The success of focused operations for pHPT guided by IPM has been excellent^{300,354,355} and in the modern era IPM helps to achieve high cure rates of 97-99% (Table 3).³⁵⁶⁻³⁶⁴ Conversely, focused operations guided solely by imaging studies without IPM can miss MGD, which occurs in about 15% of patients (Section 2) leading to failure rates that are higher than accepted standards (Section 7).^{92,365-368} However, because most patients with pHPT will have a single adenoma and because contemporary imaging studies can be quite accurate in certain settings, the routine use of IPM during focused or unilateral imaged-guided operations has

been questioned.^{240,369-371} The committee reached strong consensus that IPM is an essential intraoperative adjunct to avoid higher failure rates in image-guided focused parathyroidectomy, and that surgeons considering a focused image-guided parathyroidectomy without IPM should discuss with the patient an increased likelihood of operative failure with its attendant costs and risks. Similarly the committee reached consensus that when IPM is not available, image-guided parathyroidectomy may still be acceptable in carefully selected patients however BE remains the preferred and time-tested surgical approach.

Surgeons who routinely perform BE using IPM have noted that although intraoperative PTH levels can decrease sufficiently after removal of the image-targeted gland, anatomically enlarged glands may often remain in situ.^{304,355,372-374} Although this observation suggests that the residual enlarged glands are likely to cause persistent or recurrent disease, the reported operative success rates of focused parathyroidectomy guided by IPM are excellent^{300,356,357,359,360,375,376} and it is possible this is a phenomenon that may relate to enlarged but not yet abnormally secreting glands.^{92,357,359,360,377-379} Long-term follow-up on the order of ≥ 10 years is needed to further evaluate if focused operations guided by IPM will result in higher recurrence rates when compared to BE.

- **RECOMMENDATION 6-1-** When image-guided focused parathyroidectomy is planned, IPM is suggested to avoid higher operative failure rates.

Strong Recommendation – Moderate quality evidence

Optimizing and Interpreting IPM Data

IPM takes advantage of the short half-life of PTH (3-5 minutes) and uses a rapid immunochemiluminescence assay technique with completion times of 8-20 minutes, depending on the assay type utilized. Close proximity of the assay equipment to the operative point-of-care is ideal to avoid long turnaround times. The surgeon should be in close communication with the laboratory personnel and be aware of potential sources of laboratory error.^{375,380,381} The impact of the laboratory measurement equipment is important, as is full understanding of the manufacturer's reference ranges and calibration.^{382,383}

The accuracy of IPM is dependent upon the protocol used for blood sample collection. Surgeons should

utilize a protocol that is practical, accurate and reproducible under their local conditions.^{381,383} Intraoperative blood draws may be obtained from a peripheral intravenous line, an arterial line, or a neck vein. Central ipsilateral PTH levels have been reported to be higher than peripheral (systemic) levels and can take longer to decrease.³⁸⁴⁻³⁸⁶ Several IPM protocols have been described,^{300,353,358-361,363,387-389} and 2 commonly used and validated IPM protocols are detailed here and in Table 3. The committee reached strong consensus that the use of an established and validated IPM protocol is recommended to achieve cure rates of 97-99% in focused image-guided parathyroidectomy.

The Miami Protocol

The Miami protocol was the first method to be described and has been extensively studied.^{353,354,387} It is well validated and is in wide use today.⁹⁸ The pre-incision sample is collected in the operating room before skin incision. The pre-excision (time zero) sample is collected just prior to clamping the blood supply to the offending gland; 5 and 10-minute samples after gland resection are also collected. When the peripheral PTH value drops >50% from the highest level (either pre-incision or pre-excision) at 10 minutes after excision of the abnormal parathyroid gland(s), the procedure is stopped without further exploration. If the PTH value does not drop appropriately by 10 minutes after gland excision, the surgeon can repeat the PTH level at 15-20 minutes post-excision and in most cases, the intraoperative criterion is met with this additional measurement. If the criterion is not met after 20 minutes, further dissection should continue until additional glands are removed and the criterion is fulfilled or until a complete bilateral exploration is performed. Use of this protocol leads to excellent long-term cure rates (97-99%) (Table 3).

The Normal Range (or Dual Criteria) Protocol

First described as part of a prospective validation study for the Miami protocol, this modification is now well-validated and widely used.^{98,300,358,359,361,363} The pre-incision sample is collected in the operating room before skin incision. The second sample is collected 10 minutes after the suspicious gland or glands are removed. This method utilizes both a drop in PTH value of >50% from the pre-incision level, and a return of the PTH to within the normal range, as the dual criteria for ending surgery without further dissection. If the PTH level does not drop adequately at 10 minutes, a third sample can be sent as indicated; when both criteria

are met, the operation is concluded. Continued PTH elevation indicates further exploration. When both of criteria are met, accuracy is excellent with long-term cure rates of 97-99% (Table 3).^{300,358,359,363}

Other IPM Protocols

Several other IPM protocols have been described. In retrospective analysis, several centers have reported that when the intraoperative PTH falls >50% and into the normal range, but not <40 pg/mL, the risk of persistent or recurrent pHPT is higher.^{359,360,377} One explanation is that resection of a single adenoma would be expected to uncover suppressed PTH secretion by the remaining normal parathyroid glands. Another explanation is that the more stringent the IPM criteria, the higher the likelihood of durable cure, but also the higher the rate of BE. It should be kept in mind that during initial MIP, if the PTH levels do not fall appropriately, converting to BE is greatly preferred over a failed parathyroidectomy. This new observation will need further study prior to routine implementation.

Interpretation of PTH Dynamics

An adequate IPM drop does not define cure (Section 15) but is helpful in predicting cure. Appropriate follow-up remains necessary to conclude that the IPM predictions were in fact accurate. Prediction of postoperative normocalcemia is dependent on proper interpretation of PTH decay dynamics. Mathematical modeling techniques and software have been developed by some centers to allow surgeons to perform PTH cure analysis by determining a PTH decay curve accounting for the expected amount of PTH production by residual glands, which functions to increase MGD recognition,^{390,391} yet most surgeons will interpret IPM results without mathematical models and report excellent results^{374,390-394}

A true positive IPM result is defined as a PTH drop that correctly predicts operative cure (Section 15). A true negative result is defined as a PTH level that does not drop and correctly predicts an operative failure. A false positive result is defined as a PTH drop that meets the threshold to predict cure, but occurs in a patient who is later found to have persistent disease. False positive results are rare and may be due to unrecognized sporadic or inherited MGD, post-excision sample hemodilution or hemolysis, parathyroid carcinoma,³⁹⁵⁻³⁹⁸ or possibly to the use of specific general anesthesia agents.³⁹⁹ A false negative result is defined as a PTH level that does not drop even though the patient is cured. False negative results can be observed in patients with

decreased renal clearance, artificially elevated baseline PTH levels, baseline sample hemodilution or hemolysis, a missed PTH “peak”, or laboratory error.³⁸⁰ Surgeons using IPM should be aware of PTH decay dynamics, the pitfalls of low baseline PTH levels³⁷⁴ and the causes of false positive and false negative results, in order to maximize the probability of a successful operation.

Use of IPM in Differential Jugular Venous Sampling and Intraoperative Tissue Analysis

Differential jugular venous sampling can be used preoperatively when a hyperfunctioning gland has not been localized, or intra-operatively during a difficult exploration.^{318,319} A PTH sample is obtained from both internal jugular veins, and a unilateral PTH elevation (10% higher) indicates the side of the neck with the missing hyperfunctioning parathyroid. Conversely, similar internal jugular PTH levels suggest MGD *in situ*, or hyperfunctioning parathyroid tissue outside of the neck. Lateralization of the missing parathyroid can be expected in 70-81% of cases.^{318,319} The writing group offers the cautionary note that in reoperative parathyroidectomy, prior dissection may have ligated or disrupted venous tributaries which may alter PTH drainage patterns from missed or residual abnormal parathyroid glands. This may also impact the utility of differential venous sampling.

In resected tissues, *ex vivo* measurement of parathyroid aspirate PTH level, performed directly by the surgeon and then analyzed using an intraoperative PTH assay, can also be useful for rapid confirmation of the presence of parathyroid tissue (Section 10).^{400,401}

- **RECOMMENDATION 6-2-** Surgeons utilizing IPM should employ a sampling protocol that is reliable in the local environment and should be familiar with the interpretation of PTH decay dynamics.

Strong Recommendation - Low quality evidence

Availability and Cost

IPM is not universally available and its use does add cost to the operation.⁹³ Failed parathyroidectomy is very expensive, however, with additional costs and risks if reoperation is required.^{402,403} As stated above, the committee reached strong consensus that the failure rate of focused image-guided parathyroidectomy is greater when IPM is omitted. The value of IPM in image-localized pHPT was evaluated in a decision-tree model

analyzing cost based on the accuracy of preoperative localization studies, the cost of reoperation, the expected MGD rate, and the cost of IPM.⁴⁰² The study concluded that in well-localized patients IPM marginally increases the cure rate of focused parathyroidectomy performed without IPM guidance and incurs approximately 4% higher costs. However, when the rate of unrecognized MGD exceeds 6%, IPM was a cost-saving measure.⁴⁰²

7. MINIMALLY INVASIVE PARATHYROIDECTOMY

Definition

Approximately 85% of patients with pHPT have a solitary adenoma that can be cured with resection of a single gland (Section 2). Consequently, surgeons have adapted a variety of methods to streamline surgery and reduce complications.^{40,300,404-406} These techniques can be collectively termed minimally invasive parathyroidectomy (MIP). The current literature includes 75 different definitions for MIP.⁴⁰⁷ The committee reached consensus that all such techniques intend a limited dissection field, quick recovery from whatever anesthesia is used, and reduced postoperative discomfort. MIP is characterized by features such as short incision length (e.g. <3 cm), focused extent of dissection (e.g. typically only one gland identified), use of anesthesia techniques (e.g. local, regional and/or general) that facilitate a limited hospital stay (e.g. outpatient surgery), an increased reliance on operative technology (e.g. endoscopic) and adjuncts (e.g. IPM), and the routine use of preoperative imaging (e.g. US, sestamibi, and 4D-CT).

Limited dissection refers to avoiding any unnecessary tissue separation for purposes of exposure of the ipsilateral gland, RLN, thymus, trachea or similar structures. This requires restricting the field of dissection to that necessary to open the tissue planes around the imaged parathyroid gland.³⁴⁴ The alternative to MIP is BE (Section 8) which is a reliable approach with the ability to treat either adenoma or MGD with acceptable risk and morbidity, and which does not require preoperative imaging. Bilateral visualization of MGD using a type of minimally-invasive technique with locoregional anesthesia and conscious sedation can be achieved in the motivated patient.⁴⁰⁸

IPM and Imaging

Regardless of the MIP technique used, a limited dissection requires use of specific adjuncts and strategies to improve the probability that all hyperfunctioning glands are identified and managed appropriately to substitute for 4-gland visualization and ensure durable cure. Preoperative imaging can predict, with some degree of error, the presence and location of a parathyroid adenoma (Section 4) and is widely used to guide MIP. Concordant single-focus imaging results, although not required to pursue MIP, increase the likelihood of success.^{303,305,409-413} However, it is essential to keep in mind that, even when imaging results suggest a solitary focus of isotope, the risk of unidentified MGD remains (Section 4).^{47,414}

IPM (Section 6) has proven utility as a functional guide to detect or exclude MGD after the excision of an abnormal parathyroid gland.^{40,73,136,300,305,357,359,405,415-419} MIP in selected patients can achieve biochemical cure in approximately 97-99% when adjunctive IPM is also used to confirm adequacy of resection.^{40,300,415} One analysis of 17 studies estimated that IPM increases the success rate of MIP in patients with well-localized disease from 96.3% to 98.8%.³⁵ When used properly, IPM provides independent verification of success and reduces the rate of failure after MIP.⁴¹⁶ During MIP, if IPM suggests residual hypersecretion of parathyroid hormone, conversion to BE is an acceptable outcome in this context and is associated with favorable outcomes when compared to conventional BE.^{300,305,405}

Although MIP with IPM is a validated and widely-accepted technique today, some have voiced concerns that it is not necessary,⁴²⁰ can extend operative time,⁴²¹ adds cost, can result in missed morphologically abnormal glands^{92,93} or prompt unnecessary BE.^{422,423} However, BE is the default standard approach operatively, so the latter point is somewhat tautological. Conversely, many advocates of MIP using IPM, report shorter operative times even when taking IPM assay time into account, and report equivalent or decreased cost.³⁵ MIP has complication rates similar to BE.^{369,424} However, using the Miami protocol for IPM interpretation (Section 6) there are recent reports that long-term cure rates may be lower in MIP with IPM compared to BE, and this topic bears further investigation.^{92,357}

Probe radioguidance is an alternative intraoperative adjunct (Section 10).^{92,261,425-428} However, no studies to date have validated its utility to identify or exclude MGD without also employing IPM or BE (Section 9).

Overall the majority of the committee defines MIP by the intent to limit dissection using IPM to detect residual hyperfunctioning parathyroid tissue. The committee reached strong consensus that outside of certain expert and/or tertiary settings, MIP without IPM should be attempted only after patients are counseled about the potential for a higher rate of operative failure.

Patient Selection

Patient selection by imaging, family history, and anatomic factors is essential to achieving good outcomes with MIP. As stated above, MIP relies on use of preoperative localization studies to guide the initial surgical approach, and is ideally suited for patients who appear to have a single adenoma by imaging. Parathyroid imaging should be ordered only after biochemical diagnosis of PHPT and the decision to pursue operative intervention is established (Section 4). Although radiologists often have responsibility in the performance and interpretation of parathyroid localization studies, surgeons must take a lead role in image interpretation, since only they can correlate preoperative localization results with anticipated or actual intraoperative findings.^{167,269}

Patient selection for MIP must include consideration of the baseline risk of MGD. Contraindications for planned MIP include evidence of bilateral parathyroid disease on localization or clear evidence of familial HPT, both of which suggest the presence of MGD (Section 9). Additionally, surgeons must consider preoperative clinical factors that may predispose to MGD, e.g. age <30 (Section 7) and/or that may make parathyroidectomy difficult, including high body mass index, kyphoscoliosis, concurrent thyroid size/nodules. Prior anterior neck surgery does not prohibit MIP, nor does contralateral dense neck scarring or ipsilateral RLN dysfunction.

Relative contraindications to attempted MIP include large parathyroid tumors (e.g. >4 cm), which may be difficult to extract safely via a small incision, suspected parathyroid cancer (Section 12), or a history of lithium exposure. Because approximately 50% of patients with a history of lithium exposure have single gland disease (Section 2), they can be considered for MIP with IPM as long as the surgeon has a low threshold for

converting to BE. Although a history of childhood radiation exposure to the neck or a positive family history of pHPT may increase the risk of recurrence after MIP, it is not a contraindication to attempted MIP with IPM.^{429,430} In summary, as discussed in Section 8, BE is the preferred approach for patients with discordant or non-localizing preoperative imaging, when there is a high suspicion of MGD, when IPM is not available, or at the discretion of the surgeon.

- **RECOMMENDATION 7-1:** MIP, defined as a focused dissection, is ideally employed in patients who appear clinically and by imaging to have a single parathyroid adenoma. MIP is not routinely recommended in patients with known or suspected high risk of MGD.

Strong recommendation - High quality evidence

Identifying and Discriminating Parathyroid Tissue

Parathyroid glands can visually resemble lymph nodes, central neck fat, exophytic thyroid nodules, or the thyrothymic ligament. Although the appearance of abnormal parathyroids is well-described (Section 2), the gross visual determination of gland pathology can be challenging. Parathyroid color and texture can be useful indicators, but are subjective assessments dependent on surgeon experience. Parathyroid dimensions can be difficult to measure when a gland is surrounded by fat or the thyrothymic ligament. During parathyroidectomy, confirmation of the parathyroid nature of removed tissue can be evaluated by one or more methods.

Ex vivo aspiration of resected parathyroid tissue (Section 10) employs IPM methodology to rapidly, accurately and inexpensively distinguish parathyroid tissue from other tissues⁴⁰¹ and is particularly useful if there is poor or delayed access to frozen section analysis. Aspiration is performed with a fine needle and the tissue aspirate is rinsed into 1 cc of normal saline and sent for intraoperative PTH testing. This adjunct is highly sensitive for the identification of parathyroid vs. other cervical tissue (thyroid, thymus, lymph nodes).^{401,431,432}

Frozen section analysis (Section 10) can identify or exclude the presence of parathyroid tissue intraoperatively, and in some cases can also estimate the scarcity of intrapathyroidal fat which suggests hypercellularity.^{86-88,433,434} Routine intraoperative microscopic examination by a pathologist is controversial today and may be used, for example in centers where IPM is not readily available. The surgeon should be

cognizant that results can occasionally be misleading.^{89,245,435-437} The freezing process can sometimes cause artifacts and it has been suggested that touch imprints can increase sensitivity for diagnosis from 94-98% with frozen section alone up to 100% in combination.^{438,439} A recent study demonstrated that in patients with negative preoperative imaging there is a higher use of frozen section analysis.⁴⁴⁰

A variety of gross and microscopic findings can help to distinguish normal from abnormal parathyroid glands. Weight is the most reliable distinguishing feature of abnormality, since it is both objective and reliable.⁸⁴ In addition to discerning normal from abnormal parathyroid glands, weight <200 mg for the first resected gland may also be predictive of anatomic MGD.^{235,441} Weight determination on the final pathology report is standard and should be done for all resected parathyroid glands. However, weight determination is not a practical measure until after the gland is excised, whereas parathyroid size estimation is a surgeon-dependent skill, which is acquired with experience. Size, shape, and IPM results can also help the surgeon differentiate normal from abnormal parathyroid glands, as can the comparison of gland size and appearance. Although comparison of the first excised gland to the ipsilateral gland(s) can be useful during MIP, it is not obligatory to routinely view the ipsilateral normal gland(s).^{30,360,424} Although the point remains controversial, histologic cellularity does not reliably discern either adenoma from MGD or normal from abnormal parathyroid glands, nor is it a reliably available intraoperative parameter.^{89,245,435-437}

- **RECOMMENDATION 7-2:** *Ex vivo* PTH aspiration or frozen section analysis may be used to confirm the resection of parathyroid tissue.

Weak recommendation - Low quality evidence

Conversion to Bilateral Exploration

The intent of initial surgery is cure (Section 15) and when warranted by intraoperative findings, conversion from MIP to BE should occur during the initial surgery.^{35,300,359} Although localization studies can suggest a solitary parathyroid adenoma, anatomic heterogeneity in the form of double adenomas or 4-gland hyperplasia may still exist (Section 4).^{47,414} When an abnormal parathyroid gland cannot be found during MIP, BE to search for an abnormal parathyroid gland should be performed (Section 8). Additionally, when an un-imaged or

unexpected abnormal ipsilateral gland is encountered during MIP, this situation represents MGD, and its presence prompts conversion to BE with identification of all parathyroid glands. Lastly, in almost all cases if resection of an abnormal parathyroid gland does not result in an adequate IPM drop (Section 6), MIP should be converted to BE.

- **RECOMMENDATION 7-3:** During MIP the discovery of MGD, the inability to identify an abnormal gland, or the failure to achieve an appropriate IPM drop should prompt conversion to BE.

Strong Recommendation - High quality evidence

8. BILATERAL EXPLORATION

Felix Mandl performed the first parathyroid surgery in 1925. Shortly after that, Oliver Cope and others found that MGD was sometimes present and instituted routine bilateral exploration (BE). In BE, all four parathyroid glands should be identified in order to deduce the presence of either a single adenoma or MGD, comparing the relative sizes and appearance of the glands; abnormal glands are then resected. With the introduction of IPM in the 1990's, MIP has become increasingly favored as a surgical approach (Section 7).^{93,98,442} As a result, while BE was historically the option of choice, it is now one of 2 robust options for definitive treatment of pHPT. BE has long-term success rates of >95% and low complication rates.^{87,92,96,252,264,333,443-446}

- **RECOMMENDATION 8-1:** BE provides a time-tested standard of efficacy and safety in the definitive treatment of pHPT.

Strong Recommendation - High quality evidence

Parathyroid Embryology and Anatomy

Familiarity with parathyroid anatomy and locational variations, both eutopic (normal position) and ectopic, as well with as the gross appearance of normal and abnormal glands (Section 2), is essential for surgeons performing parathyroid surgery. The parathyroid and thymus glands arise from endodermal epithelial cells; the superior glands derive from the fourth branchial pouch and the inferior glands from the third branchial

pouch. The majority of patients have 4 parathyroid glands (2 superior and 2 inferior), although up to 13% of patients may have supernumerary (>4) glands.^{447,448} As a result of embryologic descent, the locations of the parathyroid glands can be variable (Figure 1), although the superior and inferior glands are typically (70-80% of the time) symmetric to each other.⁴⁴⁷

The superior glands descend with the thyroid and are typically located near the cricothyroid junction; as they are closely associated with the posterolateral aspect of the superior thyroid, they can sometimes be found within the perithyroidal fascia or within the thyroid. The inferior glands are in an anterior plane closely associated with the thymus and have a longer line of descent embryologically, with increased variation in their anatomic position compared to superior glands. Inferior parathyroids are located at or near the inferior pole of the thyroid (50%), or within the thyrothymic ligament (25%); the remainder can be high in the neck (undescended gland at carotid bulb) or within the mediastinum. Intrathyroidal parathyroid glands occur approximately 1% of the time.

The RLN is an important landmark in the differentiation of superior from inferior parathyroids: superior glands always lie posterior (dorsal/deep) to the RLN, usually within 1-2 centimeters cranial to the junction of the RLN and the inferior thyroid artery, while inferior glands lie anterior (ventral/superficial) to the RLN. Given the variability in gland location, despite constant anatomic relationships to the RLN, even for ectopic glands a novel classification system that identifies parathyroid glands based on the most frequently encountered locations has increasingly been utilized today.²⁷⁴

Ectopic parathyroid glands can be superior, inferior, or supernumerary in origin and their occurrence is attributed to migration during embryogenesis. Although ectopic glands have been reported to occur in up to 22% of patients undergoing parathyroidectomy for pHPT, the definition of “ectopic” varies considerably; some commonly described locations include the thymus, retroesophageal space, mediastinum, and intrathyroidal. Others consider these locations to be expected destinations of enlarged glands and reserve “ectopic” for those in less frequent locations - including a high cervical position (undescended glands) and within the carotid sheath.^{425,447-451} In addition, just like abnormal ectopic glands, abnormal supernumerary glands must be surgically managed. Supernumerary glands occur in up to 13% of adults and may be encountered during BE;

moreover if IPM is being used, the presence of an abnormal supernumerary gland occasionally may be actively deduced. During surgery, knowledge of the potential ectopic gland locations is critical to success, as multiple studies have shown that the most common reason for a failed initial parathyroidectomy is the inability to find an ectopic parathyroid adenoma.^{425,449,450,452,453}

Planned Bilateral Exploration in Sporadic pHPT

In the current era many parathyroid surgeons routinely perform MIP in patients with sporadic pHPT and positive imaging results. In 2 recent surveys of the AAES and American College of Surgeons, 68% of respondents routinely perform a focused exploration, compared to 11% of surgeons 10 years prior, while routine BE was performed by only 10%, compared with 74% 10 years earlier; as of 2011, all 19 existing Endocrine Surgery fellowships recognized by the AAES routinely taught MIP with IPM.^{93,98} Still, there is an important role for BE in patients with sporadic pHPT, which includes situations of surgeon choice, nonlocalizing imaging, high likelihood of MGD, or when IPM levels during do not meet appropriate criteria to terminate MIP (see also Section 8).^{92,93,361}

Several recent studies have suggested either that MIP may not be as sensitive as BE in recognizing MGD, that traditional weight/size criteria are faulty,^{40,92,93,236,354,415} or that institutional issues may favor BE. In a 2-institutional study, MGD, defined by weight/size rather than by function, was identified in 17% of patients who underwent routine BE compared to 11% who had a focused approach ($p=0.028$).²³⁶ Similarly, a study of 1,158 patients who underwent routine BE concluded that MGD defined by weight/size criteria would have been missed in 20% on focused exploration, despite concordant preoperative imaging results and an appropriate decrease in IPM levels using the Miami protocol.⁹³ Neither study demonstrated a difference in rates of recurrence by MIP vs. BE. A third series found that patients undergoing unilateral parathyroidectomy had a 10-year recurrence rate of 4-6%, that was 11 times higher than patients selected for BE at the same institution.⁹² A prospective randomized trial comparing unilateral (with preoperative localization and IPM) to bilateral exploration found no difference in recurrence at 5 years, but a high overall recurrence rate of 6.6%.⁴⁰⁵ A small recent study observed a significantly longer median operative time in MIP with IPM, compared to BE.⁴²¹

However, IPM performance is influenced by institutional variations in the time required to draw and transport blood and by turnaround time for the utilized assay (Section 6).

Overall the committee reached strong consensus that in most patients with discordant or nonlocalizing preoperative imaging, a planned BE is appropriate.⁴²¹

- **RECOMMENDATION 8-2:** Planned BE is the preferred operative strategy in situations of discordant or non-localizing preoperative imaging, when there is a high suspicion of MGD, when IPM is not available, or at the discretion of the surgeon.

Strong Recommendation - Moderate quality evidence

Technique

BE can be performed under general anesthesia or conscious sedation (intravenous and locoregional anesthesia).^{408,454} During BE, if preoperative imaging has localized a suspected parathyroid adenoma, that gland should be sought first. In patients managed without imaging or who have nonlocalizing results, since hyperfunctional glands are equally distributed by anatomic location both in embryologic origin and in laterality, there is no preferred side on which to begin.⁴⁵⁵ As required, the eutopic locations for superior and inferior parathyroid glands should be explored, with careful inspection of the posterior surface of the thyroid, as some parathyroid glands may be intracapsular and/or bilobed (hour-glass shaped). The RLN should be identified within the tracheoesophageal groove, both as a guide for identification of parathyroid glands and to prevent potential injury. The retroesophageal space should also be palpated and carefully inspected.

During BE, all 4 parathyroid glands should be identified and evaluated prior to decision-making about single or multiglandular disease, be it eutopic, ectopic, or supernumerary. As also discussed in Section 8, normal parathyroid glands are small, soft, and often embedded within a small fat pad; they are typically tan or ‘peanut-butter-colored’. Normal parathyroid glands weigh approximately 20-50 mg. Abnormal parathyroid glands are larger, more rounded, and often darker in color, secondary to a decrease in the proportion of adipose tissue. When gently probed, abnormal parathyroid glands may ‘push back’, rather than flattening or giving way.⁴⁵⁶

In BE, if a single gland is resected the use of IPM can help to confirm adequacy of resection, although not required if all glands are identified. If multiple parathyroid glands are found to be abnormal, subtotal parathyroidectomy (SP) is performed. The decision regarding which glands to remove in SP should be based on their size, viability, and anatomic location. Ideally, a subtotal resection entails leaving behind a portion of the gland that is most normal in consistency and size, has an easily preservable vascular pedicle, and is anteriorly located (for ease of future identification should reoperative parathyroidectomy be required). During SP the parathyroid remnant should be about 1-2 times the size of a normal gland and should remain in situ with an adequate blood supply and marked with nonabsorbable suture or surgical clip. Subtotal resection of the gland targeted as the remnant should be performed early, prior to resecting the remaining parathyroid glands, to ensure viability of the remnant.

If no abnormal parathyroid gland can be identified, ectopic locations should be explored. Consideration should next be given to cervical thymectomy and/or (rarely) to ipsilateral thyroid lobectomy. Intraoperative sampling of bilateral internal jugular vein PTH levels can also be performed (Section 6), to aid in identifying the laterality of a missing abnormal gland.³¹⁹ If no abnormal gland can be identified, normal parathyroid glands should not be removed. Sternotomy for exploration of the mediastinum is rarely required at initial surgery.

During BE all attempts should be made to delicately preserve the thyroid gland *in situ*. However in the course of parathyroid exploration it may be necessary to resect cervical lymph nodes or other structures. A thyroid lobe may require resection to improve access to an abnormal parathyroid gland, to perform *en bloc* resection of parathyroid carcinoma, to treat concomitant thyroid disease, or to resect an abnormal intrathyroidal parathyroid gland (Section 11).

- **RECOMMENDATION 8-3:** BE is defined by a standard technique in which all parathyroid glands are identified with exploration of expected and, if necessary, ectopic cervical locations.

Strong Recommendation -Moderate quality evidence

Extent of Surgery in Lithium-induced pHPT

Approximately 50% of pHPT patients with chronic lithium exposure will have single gland disease^{54,112}. Given the higher rate of MGD, BE has historically been recommended as the operative procedure of choice for patients with lithium-associated pHPT. However, more recent studies have shown that rates of MGD may be as low as 25%, with similar long-term rates of recurrence, suggesting that a focused exploration with IPM may be achievable.^{53,54,112,457-461}

- **RECOMMENDATION 8-4:** In lithium-induced pHPT, the surgical approach may be either BE, or MIP guided by imaging and IPM.

Weak Recommendation - Low-quality evidence

9. FAMILIAL pHPT

In patients with a genetic predisposition for pHPT, the high likelihood of MGD and recurrent hypercalcemia later in life necessitate a distinctive surgical approach from sporadic pHPT, with the goals of 1) achieving eucalcemia for as long as possible; (2) avoiding iatrogenic hypoparathyroidism; and (3) facilitating potential reoperation for recurrence.

Extent of Surgery in MEN1

Primary HPT occurs in >90% of patients with MEN1, with the majority having morphologically robust MGD.⁴⁶ Initial surgical options most commonly are either subtotal parathyroidectomy, or total parathyroidectomy with immediate autotransplantation, although recent studies have proposed initial unilateral clearance and thymectomy in younger patients with localized disease on imaging.^{46,62,397,446,462-467} In one study of 92 MEN1 patients undergoing parathyroidectomy, one-third developed recurrent disease in follow-up (median 5.7 years; range, 0.25-42.4) despite an initial surgical cure rate of 98%. The lowest rate of recurrence was after total parathyroidectomy with autotransplantation (23%), compared to resection of ≤ 2.5 glands (46%) or subtotal parathyroidectomy (33%). However, the incidence of severe hypoparathyroidism was higher in the total parathyroidectomy group (46%) than the subtotal parathyroidectomy group (26%).⁴⁶⁵ Similarly, a retrospective cohort review from the Dutch MEN1 database demonstrated that rates of persistent/recurrent HPT

were higher after less than subtotal parathyroidectomy (53%), compared to subtotal parathyroidectomy (17%) or total parathyroidectomy with autotransplantation (19%). Permanent hypoparathyroidism was reported to occur in 24%, 39%, and 66% of MEN1 patients, respectively.³⁹⁷ A recent prospective randomized trial demonstrated a 24% recurrence rate after subtotal parathyroidectomy vs. 13% after total parathyroidectomy with autotransplantation.⁴⁶⁶

In general there is little role for initial MIP in patients with MEN1-related pHPT. However, the time to recurrence is not well-studied and since younger patients may not develop recurrence for many years, if preoperative imaging demonstrates a single focus of disease that is confirmed during parathyroidectomy with an adequate drop in IPM, less than subtotal parathyroidectomy may be considered¹²⁰. An alternative approach under study is unilateral clearance of both parathyroid glands and the cervical thymus, so that later reoperation will likely be limited to the contralateral side.⁴⁶⁷⁻⁴⁶⁹ Overall, due to the higher risks of permanent hypoparathyroidism following total parathyroidectomy (there can also be technical problems at the forearm autograft site) and the higher risks of persistent/recurrent pHPT after MIP in MEN1,^{46,462,470} the committee reached strong consensus that subtotal parathyroidectomy is the recommended initial approach in MEN1 patients.

Transcervical thymectomy should be considered in all MEN1 patients given the risk of supernumerary parathyroid glands present in the thymus, particularly if all four parathyroid glands were not yet managed.^{46,462,470,471} Transcervical thymectomy also has been recommended to reduce the risk of developing thymic neuroendocrine tumor.^{46,472} However, the effectiveness of this approach has been challenged, given that most transcervical thymectomies will not remove the entire thymus and studies have not shown that it prevents the development of malignant thymic neuroendocrine tumor.^{470,473}

- **RECOMMENDATION 9-1:** In patients with MEN1-associated pHPT, subtotal parathyroidectomy is recommended as the index operation.

Strong Recommendation - Moderate quality evidence

Extent of Surgery in MEN2A

Patients with MEN2A express pHPT only 20-30% of the time, depending on the particular RET codon mutation and its known genotype-phenotype relationship; for example pHPT is almost always present in patients with exon 11 mutations (RET codon 634) and less frequently in patients with exon 11 mutations (RET codons 609, 611, 804).^{45,65} In recent studies pHPT in MEN2A may be mild and is often asymptomatic.^{474,475} Also, unlike in MEN1, in MEN2A the parathyroid glands are morphologically heterogenous. Thus the surgical management in MEN2A can be challenging, especially given the risk of hypoparathyroidism associated with initial or reoperative thyroidectomy for medullary thyroid cancer in this disorder. The extent of parathyroidectomy may also depend on whether previous thyroidectomy has been performed. In MEN2A patients undergoing prophylactic thyroidectomy for medullary thyroid cancer, serum calcium levels should be obtained prior to surgery.

Surgical options include: (1) resection of only visibly enlarged parathyroid glands; (2) subtotal parathyroidectomy, with 1 gland or a portion of 1 gland left *in situ*; or (3) total parathyroidectomy with immediate heterotopic autotransplantation.^{446,476,477} In a study of 119 MEN2A patients, persistent or recurrent pHPT occurred only after selective (9%) or subtotal (14%) resection, with an equivalent rate of permanent hypoparathyroidism after subtotal vs. total parathyroidectomy (29% vs. 20%, respectively) providing a rationale for total parathyroidectomy with forearm autograft.⁴⁷⁷ However, in a separate study of 56 MEN2A patients, cure was achieved in only 89% irrespective of the extent of resection; 11% had persistent pHPT and 9% had recurrent pHPT in follow-up of 6.4 years, combined with a 22% rate of hypoparathyroidism, and the authors concluded that resection of only macroscopically enlarged glands is sufficient.⁴⁷⁸

With the evolution of techniques for IPM and MIP, in patients with MEN2A-associated pHPT who have not had previous neck surgery, resection of only the visibly enlarged glands is typically performed today. If all glands are abnormal, subtotal parathyroidectomy is preferred and in patients at high-risk for recurrent MTC, autotransplantation should be considered. If a normal gland is devascularized and/or the patient has a codon mutation that is not commonly associated with pHPT, consideration can be given to parathyroid autotransplantation within the neck. Otherwise, forearm autotransplantation should be performed.^{45,446,474}

- **RECOMMENDATION 9-2:** In MEN2A-associated pHPT, resection of only visibly enlarged glands is recommended.

Weak Recommendation - Low quality evidence

Extent of Surgery in Other Familial Forms of pHPT

The extent of parathyroidectomy in patients with HPT-JT (Sections 1) or familial isolated HPT (FIHPT) is controversial, particularly since these diagnoses are often not known at the time of initial surgery. In one recent study of 3 FIPHT families, 12 patients underwent BE but only macroscopically enlarged glands were resected. One patient had parathyroid carcinoma and 3/11 patients who had apparent single adenoma developed recurrent disease 5, 9, and 27 years later, indicating unrecognized MGD.⁴⁷⁹

Similarly, in a study of 3 HPT-JT kindreds with 30 years of follow-up there was a high persistent/recurrent pHPT rate of 80% after initial parathyroidectomy, which primarily consisted of resection of only enlarged glands.⁴⁸⁰ A separate study of 3 HPT-JT kindreds found that resection of a single parathyroid gland was followed by a recurrence rate of 17% after a mean disease-free interval of 13.7 years.⁴⁸¹ These data suggest that subtotal parathyroidectomy is the appropriate initial procedure in known HPT-JT. HPT-JT patients are also at higher risk for parathyroid carcinoma (PCA). A recent study of 7 unrelated kindreds identified PCA in 38% of patients.⁴⁸²

Therefore, while the optimal surgical approach for HPT-JT and FIHPT remains undefined, at the time of surgery in patients known to have these disorders, surgeons should have a high suspicion for MGD as well as for PCA requiring *en bloc* resection (Section 12).^{124,483} Lifelong postoperative follow-up is especially critical in both these familial conditions.

10. SURGICAL ADJUNCTS

The information in this section is meant to act as a supplement for surgeons who are already well versed in the technique of parathyroidectomy.

Intraoperative adjuncts can be helpful or reassuring to the surgeon in achieving cure. The most widely used intraoperative adjunct is IPM (Section 6). Adjuncts can also assist with confirmation of resected parathyroid tissue (frozen section analysis, *ex vivo* parathyroid aspiration (Section 7)), visualization of glands (methylene blue, near infrared fluorescence/infrared spectroscopy), and anatomic localization of glands (intraoperative US, bilateral jugular venous sampling, radioprobe guidance). Recurrent laryngeal nerve monitoring is used less frequently in parathyroidectomy than thyroidectomy, but may play a role in reoperative procedures. Unique surgical approaches play a limited role (videoscopic or robotic parathyroidectomy). Adjuncts cannot replace judgment and experience, and in many cases the data supporting their use are limited.

Confirmation of the Identity of Resected Parathyroid Tissue

In the ideal MIP, after preoperative localization identifies an apparent single gland for resection, the surgeon finds and removes a classically appearing parathyroid adenoma, intraoperative PTH levels normalize, the operation is concluded, and long-term follow-up laboratory results show cure. However in any scenario the surgeon may need confirmation that the resected tissue is parathyroid in origin, particularly to help guide the need for additional dissection and resection of abnormal glands. The most commonly used adjuncts for tissue confirmation are frozen section analysis and fine needle aspiration with PTH assay (Section 7).

Adjuncts to Enhance Visualization of Parathyroid Glands

Normal and aberrant parathyroid anatomy is described in Section 2. Use of several dye types have been described during surgery to assist in parathyroid identification, although none are used commonly. The most often used dye is methylene blue, which was first reported in 1971 (1). Normal parathyroid glands contain fewer oxyphilic cells, which is hypothesized to lead to less dye uptake than in adenomas or hyperplastic glands.^{484,485} Methylene blue is generally administered at 5-7.5 mg/kg of patient body weight diluted in 500 cc of lactated ringers as an infusion for 45-60 minutes preoperatively.^{485,486} However in a 2012 meta-analysis of 39 observational studies, while most showed some efficacy in staining abnormal parathyroid glands, its effectiveness for routine identification of normal parathyroid glands was not demonstrated.⁴⁸⁷ Methylene blue has known potential toxicities of severe hypertension, headache, fever, confusion, and hemolytic anemia in patients with glucose 6 phosphate dehydrogenase deficiency, and its binding to hemoglobin can also interfere

with pulse oximetry during surgery. Its use is contraindicated in pregnant patients and the drug is FDA-approved only for the treatment of drug-induced methemoglobinemia.⁴⁸⁸

Other adjuncts for intraoperative gland visualization expose the parathyroid glands to varying light wavelengths with or without photosensitizing agents or near infrared fluorescence or autofluorescence.⁴⁸⁹⁻⁴⁹¹ While these techniques have been successfully used during parathyroid surgery, they are experimental; near infrared spectroscopy equipment is still under development and not available for routine use.⁴⁹²

Adjuncts to Enhance Gland Localization

Intraoperative Ultrasound

Intraoperative ultrasound (IOUS) is a longstanding adjunct that is often part of an experienced surgeon's armamentarium for difficult exploration.^{468,493,494} IOUS is noninvasive, is particularly helpful in reoperation, may yield additional intraoperative information, can help with incision placement for undescended glands, and can be used to discern gland location and map surrounding tissue with the patient in the hyperextended, intubated position. Use of smaller footprint probes can access unique locations or provide a different viewing angle that would otherwise be unavailable. Although the adjunct is in common use there is surprisingly sparse current literature on its efficacy.

Jugular Venous Sampling (JVS)

Another common use of IPM is to help guide the laterality of dissection to find a missing hyperfunctional gland (Section 6).^{319,494-497} JVS by IPM is simple to perform and may yield additional intraoperative data, e.g. the lack of a gradient may signify a mediastinal gland. Today the use of JVS fully supplants the invasive modality of selective venous sampling, which for difficult parathyroid reoperation was performed in an interventional radiology suite and required central venous access with placement of multiple fluoroscopic catheters (Section 4, Section 17).

Probe Radioguidance

Technetium 99-m is the nuclear medicine tracer administered during sestamibi scanning for the localization of hyperfunctioning parathyroid tissue; as discussed in Section 5 it has imperfect specificity and sensitivity particularly for MGD, with a high false positive rate of uptake in thyroid tissue as well.^{269,275,297} This

same tracer can also be used as an intraoperative adjunct to help locate hyperfunctioning parathyroid glands. An injection is given on the morning of the planned operation, usually 1-2 hours prior to surgical intervention. To direct the dissection intraoperatively, a handheld gamma probe may be intermittently brought into the field and used with an audible device quantifying gamma activity. Upon resection of parathyroid tissue, an *ex vivo* gamma assessment confirms resection of concentrated radioisotope and may serve as a surrogate of hyperfunctional gland removal. A gamma count can also be obtained of the resection bed to suggest removal of concentrated isotope. Probe use is advocated to serve as a surrogate for either hyperfunction assessment by IPM (Section 6) or for visual size/weight comparisons by BE (Section 8); a 20% drop in gamma emission from *ex vivo* to bed is taken to signify the resection of an abnormal parathyroid gland.^{426-428,498-500} Because thyroid and cardiac tissue (the historical use of isotope) also have sestamibi uptake, specificity is variable.

In initial studies of initial surgery in selected patients, this adjunct was reported to have 97-99% successful localization of abnormal parathyroid tissue that when resected, resulted in cure of pHPT.⁵⁰¹⁻⁵⁰³ However, one group that had strongly advocated probe use without IPM recently reversed their position due to observed high rates of recurrent pHPT.^{92,504} Other groups have investigated to report questionable utility particularly in initial surgery.^{505,506} Although this adjunct has with good success when used together with IPM,⁵⁰² to date no studies have validated its independent utility in identifying or excluding MGD without also employing IPM or BE.

Recurrent Laryngeal Nerve Monitoring

RLN monitoring has been used during thyroid surgery and less frequently during parathyroid surgery to assess the RLN for function and to assist with nerve localization in difficult cases (e.g. reoperation); it has also been proposed for use by low-volume surgeons (<45 nerves at risk/year).⁵⁰⁷ However, after over a decade of study in thyroidectomy the technique has not been shown to decrease the rate of RLN injury as manifested by transient vocal cord palsy or permanent vocal cord paresis⁵⁰⁸⁻⁵¹¹ including a recent large meta-analysis of almost 24,000 patients.⁵¹² In studies of combined thyroid and parathyroid surgery utilizing this tool, only 2.8-20% underwent parathyroid procedures thus while the adjunct may play a role in reoperation (Section 17), in primary

parathyroidectomy it has not been shown to be add to visual assessment of the RLN in keeping the rate of injury low.^{513,514}

Unique Surgical Approaches

Although MIP and BE (Section 7, Section 8) are the current standard surgical approaches in patients with pHPT, other techniques have evolved in selected patients. Neither video-assisted parathyroidectomy nor robotic parathyroidectomy is a widely performed procedure today.

As a part of the rapid advances of minimally invasive surgery in the 1990's, the first total endoscopic parathyroidectomy was performed in 1996.⁵¹⁵ One version of this approach utilizes CO₂ insufflation and lateral incisions for port placement. Video-assisted parathyroidectomy utilizes a small incision, modified retractors instead of CO₂ insufflation, and a narrow video-endoscope; in a review of over 500 cases, the approach was successfully completed in 94% with a cure rate of 98% in mean follow-up of almost 3 years⁵¹⁶ with similar operative time and complication rates to conventional MIP. One study that quantified the significant learning curve also reported a 1 in 7 conversion rate to conventional MIP.⁵¹⁷ Video-assisted parathyroidectomy typically involves unilateral dissection in selected patients but can be done as a bilateral dissection.^{518,519 517,520}

In many disciplines surgeons are now utilizing robotic systems to assist with visualization and dissection in small, technically challenging body locations. There are currently about 35 case reports on robotic parathyroidectomy for highly selected patients. This complex procedure requires specialized, costly equipment, lengthy operative time, a steep learning curve, and is generally carried out through an axillary incision to aid cervical cosmesis (today's short MIP incisions may render such a rationale questionable.) Robotic parathyroidectomy has added costs^{521,522} without long-term data on outcomes or complication profiles. The technique is not FDA-approved.

Overall, surgical adjuncts to parathyroidectomy are currently unproven, but may be considered depending on the individual surgeon's practice and preferences.

11. CONCURRENT THYROIDECTOMY

Thyroid resection at the time of parathyroidectomy may be performed for suspicion of parathyroid cancer (Section 12), removal of an abnormal intra-thyroidal parathyroid adenoma, improved access, or for the presence of concomitant thyroid disease requiring resection.

Epidemiology

Thyroid nodules are a common occurrence and can be found in up to 20-50% of the US population.^{523,524} Only 5% of thyroid nodules will harbor a malignancy.^{278,525,526} After the first case of concomitant thyroid disease (myxedema) and hyperparathyroidism was reported in 1947⁵²⁷, in the mid-1950's 2 series described the incidence of thyroid nodules and thyroid cancer in patients undergoing evaluation and treatment for pHPT.^{528,529} Since that time numerous studies have documented this relationship. With the wide adoption of techniques for MIP, the phenomenon of co-existing thyroid and parathyroid disease has taken on particular importance. In patients with pHPT, the rate of concomitant thyroid disease has been reported to be 12 – 67% with the rate of concomitant thyroid cancer as high as 24%; most modern series report a cancer rate of 2-17.6%.^{184,530-538} Up to 58% of these thyroid malignancies are microcarcinomas.⁵³⁰ As might be expected due to the relative prevalences, the rate of concomitant pHPT in patients seen primarily for thyroid disease is <0.3-5%, which even so is approximately 3 times the risk for the general population.^{278,539,540} While physical exam may detect obvious thyroid disease, imaging techniques such as US or 4D-CT have greater specificity and much greater sensitivity.⁵⁴¹ Overall the committee reached strong consensus that while not yet standard care, thyroid imaging is reasonable and acceptable prior to parathyroid surgery. See Recommendation 4-3.

- **RECOMMENDATION 11-1:** Patients undergoing parathyroidectomy should have pre-operative thyroid evaluation due to the high rate of concomitant disease, which may require thyroid resection.

Strong Recommendation - Moderate quality evidence

Importance of Assessing Concomitant Thyroid Disease

Compared to intraoperative evaluation, preoperative assessment of thyroid nodules leads to a higher sensitivity for discovery and a lower rate of un-indicated thyroid resection than does intraoperative evaluation alone. Thyroid examination during BE without preoperative US has been found to miss thyroid nodules <1cm and nodules 1-2 cm up to 94% and 50% of the time, respectively.⁵²³ Even more problematic is the fact that uncovering thyroid nodules only intraoperatively, leads to a higher rate of resection; in a large retrospective review, patients who did not have a preoperative US had a 30% rate of thyroid resection while those who had preoperative US had a 20% rate of FNAB with a subsequent 6% rate of reoperative resection.⁵³⁵ A recent prospective multi-institution study found that 57% of patients undergoing parathyroidectomy had a thyroid nodule on preoperative US, which led to a 56% rate of FNAB and thyroid resection in 17%.⁵⁴² Ultimately, 6% of this cohort had thyroid cancer.

Preoperative identification of thyroid pathology requiring resection, especially thyroid cancer, prevents future reoperation. While subsequent thyroid surgery after parathyroidectomy is certainly possible, a number of studies have documented an increase in morbidity in the reoperative setting. In particular there is a significant increase in the rate of RLN injury (up to 12%) and hypocalcemia (up to 15%) in the reoperative setting compared to rates of <1% in a first time thyroid operation.^{249,543-546} The cost associated with reoperative surgery and the increased rate of morbidity are likely to be considerable.

- **RECOMMENDATION 11-2:** In patients with concomitant pHPT and thyroid disease requiring resection, thyroid resection should be performed at the time of parathyroidectomy.

Strong Recommendation -Moderate quality evidence

Evaluation of Concomitant Thyroid Disease

In pHPT the work-up of concomitant thyroid disease should be the same as for isolated thyroid disease in patients without pHPT. This evaluation should follow an evidence-based algorithm such as the Revised American Thyroid Association Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer,⁵⁴⁷ National Comprehensive Cancer Network⁵⁴⁸ or other similar guideline.

Preoperative FNAB should not be performed routinely for an obvious parathyroid adenoma identified on US (Sections 4 and 12) and should be avoided especially if there is high suspicion for parathyroid cancer. If an apparent thyroid nodule meets size or sonographic criteria for FNAB, consider sending the aspirate sample for PTH levels, as the nodule may actually be a parathyroid adenoma. Parathyroid adenomas may be misinterpreted as atypical follicular thyroid tumors on cytology.

- **RECOMMENDATION 11-3:** Evaluation for concomitant thyroid disease in patients undergoing parathyroidectomy for pHPT should follow evidence-based guidelines.

Strong Recommendation - High quality evidence

Indications for Concomitant Thyroidectomy

Aside from a suspicion of parathyroid cancer with local invasion, the known or suspected presence of an intrathyroidal parathyroid adenoma, and a need for improved access during parathyroidectomy, the indications for thyroidectomy in the setting of pHPT are the same as those for patients with isolated thyroid disease. The decision to perform a concomitant thyroidectomy should follow an evidence-based algorithm such as the Revised American Thyroid Association Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer,⁵⁴⁷ National Comprehensive Cancer Network⁵⁴⁸ or other similar guideline.

Careful consideration of the pros and cons of total thyroidectomy is warranted in situations where there is a potential need to reoperate in the dissected field based on final thyroid pathology. Examples of such a situation include when the thyroid disease to be resected is contralateral to the parathyroid disease or when performing a BE. A thoughtful discussion should be had with each individual patient weighing the known increased risk of reoperation in the setting of scar tissue.

- **RECOMMENDATION 11-4:** The indications for thyroidectomy for concomitant thyroid disease during parathyroidectomy for pHPT are the same as those for patients with isolated thyroid disease and should follow evidence-based guidelines.

Strong Recommendation - High quality evidence

12. PARATHYROID CARCINOMA

Presentation and Diagnosis

Parathyroid carcinoma (PCA) is the rarest endocrine tumor, yet all experienced parathyroid surgeons eventually encounter the disorder. Based on retrospective data, PCA accounts for approximately 1% of all cases of HPT.⁵⁴⁹ Approximately 3% of PCAs are nonfunctional.^{255,550} Retrospective studies have demonstrated consistent demographic and clinicopathologic patterns. The studies listed in Table 4 include >50% of cases reported to date and show equal distribution between males and females.

The presenting signs and symptoms of PCA overlap with benign pHPT, and are largely due to the hypersecretion of PTH rather than mass effect or invasion. In fact, PCA is often diagnosed only after recurrence or metastasis is identified.^{551,552} However the preoperative calcium level in PCA often far exceeds that observed in benign disease and multiple series have reported average serum values exceeding 14.0 mg/dL. Serum PTH levels are also typically high (Table 4).

Skeletal and renal symptoms are more common in PCA than in benign pHPT, while the nonspecific symptoms are typical of pHPT.^{181,553,554} Uncommonly, PCA patients present with symptoms from mass effect and invasion by the primary tumor, including hoarseness from invasion of the RLN. Approximately 31-45% of patients have a palpable neck mass, but a concomitant palpable thyroid nodule in the setting of benign pHPT is much more common than is PCA.⁵⁵³⁻⁵⁵⁵ The average size of PCA is 3.3 cm, which is larger than most benign parathyroid adenomas.^{556,557} Therefore, preoperative imaging results showing a large parathyroid tumor should increase suspicion of PCA.

Percutaneous needle biopsy cannot reliably distinguish benign or atypical parathyroid enlargement from PCA. Although some reports have suggested that percutaneous sampling of benign parathyroid adenoma is safe,^{291,292} the theoretical risk of malignant cell dispersion exceeds the potential diagnostic value and several cases of needle tract metastases from PCA have been reported.⁵⁵⁸⁻⁵⁶⁰ Parathyroid biopsy can also result in hematoma formation, abscess, and inflammation that can increase the difficulty of subsequent surgical exploration and complicate the histopathological examination by creating artifact that can mimic PCA in benign lesions.²⁹³ Thus, when PCA is suspected, diagnostic percutaneous biopsy should not be performed.

- **RECOMMENDATION 12-1:** The diagnosis of PCA should be considered in patients with pHPT with markedly elevated PTH levels and severe hypercalcemia.

Strong Recommendation – Low quality evidence

Surgical Treatment

Since clinicians often cannot diagnose malignant parathyroid enlargement from preoperative findings, the intraoperative discovery of PCA may occur. Surgical resection is the only curative treatment for PCA and initial resection is the best opportunity to achieve a curative outcome. Thus, surgeons performing exploration for pHPT should be prepared to identify and treat PCA encountered during dissection. The intraoperative discovery of a white/gray, firm, hypervascular, or fibrotic mass that is adherent or fixed to surrounding structures should prompt complete en bloc resection if possible, which depending on tumor extent can require resection of thyroid tissue, muscle, esophagus or the RLN. In these circumstances it is important to suspect PCA until proven otherwise. Although the distinction between an atypical adenoma and PCA can be difficult based on gross features, the risks of resection in what proves histologically to be a non-malignant adenoma are usually acceptable in this context.

When PCA is suspected intraoperatively, care must be taken to avoid entering the parathyroid tumor capsule to prevent seeding and local recurrence.⁵⁶¹ This may require the *en bloc* resection of a thyroid lobe, strap muscle, or the RLN. When there is gross evidence of tumor invasion into the esophagus, a staged procedure with referral to a tertiary or quaternary center should be considered.

Reported rates of cervical lymph node metastasis from PCA range from 0% to 19%.^{109,562} In a recent review of the literature of 972 PCA cases, lymph node metastases were found in only 6.5%. One large retrospective study that included 114 patients with lymph nodes resected demonstrated that lymph node status was not associated with disease-specific survival.⁵⁶³ There is no role for prophylactic lymph node dissection or radical resection of adjacent uninvolved tissue, since these unnecessary maneuvers increase morbidity without improving patient survival. Reoperation is feasible for persistent or recurrent PCA, but scarring and anatomic

distortion increase the risk of surgical complications. Ultimately, the best chance for achieving cure is during the initial surgery.

- **RECOMMENDATION 12-2:** With intraoperative suspicion of parathyroid carcinoma, complete resection avoiding capsular disruption improves the likelihood of cure and may require *en bloc* resection of adherent tissues.

Strong Recommendation – Low quality evidence

- **RECOMMENDATION 12-3:** Prophylactic central or lateral neck dissection should not be performed for parathyroid carcinoma.

Insufficient

Pathologic Features

PCAs and atypical parathyroid adenomas are difficult to distinguish grossly and histologically from benign parathyroid neoplasms. Microscopic examination of the surgical pathology specimen may reveal fibrosis, nuclear atypia, increased mitotic activity, necrosis, capsular penetration, lymphatic or vascular invasion.⁵⁶⁴ Each of these histologic features is not always observed in PCA and none except unequivocal angioinvasion is specific for the diagnosis.⁵⁶⁴ The microscopic identification of angioinvasion or metastasis is diagnostic, but not always found in PCA.⁵⁵⁴ Since the presence of local invasion can be mimicked by fibrosis following biopsy of a benign lesion, it is not specific for PCA.²⁹⁵ A number of studies have proposed biomarkers of PCA and a recent study has confirmed the previous suggestion that Ki-67, parafibromin, Rb (retinoblastoma gene), and p27 are valuable in the histologic diagnosis of PCA.⁵⁶⁵ Loss of heterozygosity has also been studied as a predictor of PCA malignancy.⁴⁷

Parathyroid atypia (e.g. atypical parathyroid adenoma) signifies a parathyroid tumor with histologic features suggestive of PCA, but not enough histologic evidence to definitively diagnose carcinoma. The pathologic diagnosis of parathyroid atypia versus carcinoma also requires consideration of the overall picture, in particular, the intraoperative findings. The above markers are helpful to discern PCA from atypical adenoma but

no one marker has proven to be highly sensitive and specific. Intraoperative frozen section analysis cannot reliably discern benign from malignant parathyroid lesions. When PCA is suspected, intraoperative frozen section analysis is not required.

- **RECOMMENDATION 12-4:** The histologic diagnosis of PCA relies on identification of unequivocal angioinvasion and can be assisted by biomarkers.

Strong Recommendation – Moderate quality evidence

Palliative Management

PCA patients may suffer from acute hypercalcemic crisis, and both palliative medical management and preoperative preparation for resection of PCA may require control of severe hypercalcemia, for which the basic treatment principals include correction of dehydration, increasing renal calcium excretion, inhibition of bone resorption, and treating the underlying cause (Section 5).³⁴⁸ After resuscitation and furosemide diuresis, intravenous bisphosphonate infusion can provide a rapid drop in serum calcium concentration but with rare exception, this effect is transient.^{276,566} Oral bisphosphonate therapy has minimal effects on calcium concentration in PCA.

Palliative interventions for chronic hypercalcemia secondary to unresectable PCA include surgical debulking, calcimimetics and hemodialysis. Most patients with hypercalcemia from PCA respond to calcimimetic agents, such as cinacalcet, which serves as a palliative measure to reduce calcium levels.¹⁶² Patients with unresectable PCA often receive bisphosphonates in combination with calcimimetics to control severe hypercalcemia. Infrequently, refractory hypercalcemia secondary to PCA requires hemodialysis.

Systemic and Site-Directed Anticancer Therapies for Advanced PCA

Common sites of PCA metastatic disease are lung, bone or liver. PCA is generally resistant to systemic cytotoxic therapy or immunotherapy.^{554,567} Although prospective data are lacking, a few case reports have described objective tumor response or improvements in biochemical parameters after chemotherapy.^{568,569} Current research protocols for advanced PCA include molecular profiling to search for actionable targets to

guide systemic therapy. Prospective randomized studies to test systemic anticancer therapies in PCA are lacking.

There are no reports of curative outcome after external beam radiation. A few reports suggested that adjuvant external beam radiation after resection can decrease local recurrence,⁵⁷⁰ but other series indicate that adjuvant radiotherapy does not improve control.⁵⁵⁵ Importantly, external beam radiation can significantly increase the difficulty of subsequent surgical exploration. Chemical ablation by ethanol injection has been reported with limited utility.⁵⁷¹

- **RECOMMENDATION 12-5:** Adjuvant external beam radiation should not be routinely given after surgical resection of PCA and is reserved as a palliative option.

Strong Recommendation – Low quality evidence

Postoperative Surveillance

Although some PCAs demonstrate aggressive local invasion and a propensity to metastasize to distant sites, PCA encompasses a spectrum of disease that extends from indolent to aggressively metastatic tumors. The 5- and 10-year overall survival rates for PCAs are 85.5% and 49.1%, respectively.⁵⁵⁶ In the largest analysis of PCA to date, tumor size and lymph node status were not independently predictive of recurrence or survival.⁵⁵⁶ In the largest analysis that included time to recurrence, the median time from surgery to recurrence was 33 months.⁵⁵² From the Swedish Cancer Registry data, the serum calcium, extent of operation, histopathology, p90 and ploidy status were predictive of recurrence. Patient age, extent of operation, and histopathology were predictive of survival.

Biochemical screening for recurrence is best achieved with serum calcium and parathyroid hormone levels at 3-6 month intervals following attempted curative surgery. This does not pertain to the small percentage of PCAs that are nonfunctional. When biochemical screening results are positive, potentially useful imaging studies include cervical US, CT, sestamibi, MRI and PET scanning.

- **RECOMMENDATION 12- 6:** Patients with functional PCA should undergo regular surveillance by serum calcium and PTH testing.

Strong Recommendation – Low quality evidence

13. AUTOTRANSPLANTION AND CRYOPRESERVATION

Immediate Autotransplantation

Parathyroid autotransplantation is the most reliable method to preserve parathyroid function when a gland cannot be kept viable on its native vascular pedicle.⁵⁷² Immediate autograft viability rates exceed 90%.⁵⁷³⁻⁵⁷⁵ The goal of immediate autotransplantation is to preserve the function of parathyroid tissue to minimize the possibility of permanent hypoparathyroidism which otherwise renders the patient dependent upon lifelong calcium and calcitriol supplementation. All efforts should be made to preserve the maximal amount of normal parathyroid tissue and “to treat each parathyroid gland as carefully as if it is the last.”

Parathyroid ectopia or other factors may not allow the surgeon to identify or preserve all glands. It can be difficult to confirm adequate perfusion of a normal parathyroid gland once it has been manipulated and appearance is not always a reliable method.⁵⁷⁶ In the event that a gland appears to be devascularized, 2 methods have been described to help estimate viability.⁵⁷⁷ The first is to pierce the capsule with a fine gauge needle and observe for active oozing. The second is to incise the capsule with a scissors or scalpel. In either case, brisk red oozing indicates there is continued arterial perfusion, whereas a transient release of dark blood is not an indication of viability.

Autotransplantation is indicated when there is concern regarding the viability of normal parathyroid tissue in situ. The arterial perfusion of parathyroid glands that have been manipulated but are left in-situ should be assessed. If arterial perfusion appears to have been compromised, the gland should be immediately autotransplanted.^{578,579} Immediate autotransplantation is also indicated when a normal parathyroid gland has been removed along with a surgical specimen, as long as the tissue is still sterile. Surgical specimens from the central compartment should always be inspected before being sent off the sterile field to identify and manage devascularized normal parathyroid tissue. Immediate or delayed autotransplantation (below) may also be used

to move parathyroid tissue to an extracervical site in complex or inherited cases of pHPT where MGD is expected and recurrence rates are high^{575,580,581} (Section 9). The technical details of autotransplantation are beyond the scope of this guideline but the reader is referred to a review article on parathyroid autotransplantation.⁵⁸²

- **RECOMMENDATION 13-1:** Immediate autotransplantation is recommended for normal parathyroid glands that appear devascularized.

Strong Recommendation - Low quality evidence

Before autotransplantation it is prudent to confirm that tissue being autotransplanted is actually parathyroid tissue (Section 10). Although with experience surgeons may in some cases be able to accurately identify parathyroid glands by visual inspection, histologic evaluation via frozen section of a small (1-2 mm) portion of the tissue can aid when the nature of a specimen is in doubt⁵⁷⁹ and can also prevent the unintentional autotransplantation of benign or malignant thyroid tissue, thymic tissue, or lymph nodes. Marking the site of parathyroid autotransplantation with a permanent suture or clip is recommended for later identification in circumstances of recurrent disease.⁵⁸³ Additional methods to confirm the presence of parathyroid tissue are under investigation (Section 10).

Cryopreservation

In the early 1970's the technique of parathyroid cryopreservation was developed to freeze and store parathyroid tissue harvested from initial parathyroid resection.^{582,584} The tissue can then later be thawed and autotransplanted in the event of prolonged or permanent hypoparathyroidism^{573,574,585} in a procedure termed delayed autotransplantation.⁵⁸⁴ The primary indication for cryopreservation is when, upon completion of surgery, it is uncertain that there is an adequate functional residual parathyroid cell mass *in vivo*.²⁴² Common settings where there is high risk of permanent hypoparathyroidism include total parathyroidectomy for MEN1 (Section 9), and reoperative surgery. The technique of parathyroid cryopreservation^{573,586} is beyond the scope of this guideline, but in general requires a detailed protocol executed by an experienced team to ensure sterility and proper handling during preparation, freezing, thawing, and at the time of reimplantation. The materials and

manpower required for a successful cryopreservation program may not be available to surgeons who perform parathyroidectomy infrequently. Cryopreservation is not considered standard care, and the inability to cryopreserve parathyroid tissue should not discourage institutions that do not have access to the process from performing parathyroid surgery. However, in cases of reoperative parathyroidectomy or planned subtotal or total parathyroidectomy, initial referral to a center with access to this technique may benefit the patient. Thus, cryopreservation of parathyroid tissue should be considered during a parathyroid operation with a significant risk of permanent hypoparathyroidism.

Delayed autotransplantation of cryopreserved tissue has a higher rate of primary nonfunction (50-70%) than immediate autotransplantation.^{585,587} In a single center study, in over 100 human parathyroid tissue samples, viability of samples cryopreserved ≤ 24 months was 71% (10/14) vs. 1% (1/92) for specimens stored >24 months ($p < 0.001$).⁵⁸⁸ Other studies verify this concept and also point out that while resected parathyroid tissue may be cryopreserved routinely, it is uncommon that it is utilized for reimplantation.^{85,242,589,590}

14: IMMEDIATE POSTOPERATIVE CARE

Important topics concerning the immediate postoperative period include documentation, the time interval of observation for problems such as hematoma and hypocalcemia, the timing of follow-up, and the need for supplementation with calcium and/or vitamin D. While the following guidelines are broadly applicable to patients undergoing parathyroidectomy, patients with a higher level of complexity may require significant variations in these recommendations.

Operative Note

Accurate documentation of the operative findings and events of parathyroidectomy is essential. The detailed summary plays a crucial role in informing the entire care team of the conduct of the procedure. It is the key resource document for planning any subsequent neck surgery and is essential to make potential remedial parathyroid surgery safe and successful. In particular the surgical report serves as reference to the exact location of resected parathyroid glands and in this regard the use of language that is transparent, uniform and consistent

is desirable. A standard nomenclature system that succinctly describes the location and embryologic origin of each diseased parathyroid gland may facilitate communication between specialists (radiology, nuclear medicine, surgeons, pathology and endocrinology)^{591,592}

Critical components to document include:

1. Type of anesthetic technique used
 2. Approach: e.g. MIP, BE, reoperative
 3. Visualized glands: Describe the precise location in relation to the recurrent laryngeal nerve, gross appearance, and final status of the gland (e.g. removed, shave-biopsied, viable *in situ*). Describe frozen section, IPM, and/or *ex vivo* PTH aspiration results, and note if any parathyroid tissue was autotransplanted or cryopreserved.
 4. Locations explored
 5. Conduct and results of IPM (Section 6)
 6. Concurrent procedures (Section 11) and use of other adjuncts (Section 10)
 7. Other intraoperative events (e.g. thyroidectomy, RLN injury).
- **RECOMMENDATION 14-1:** The operative note should detail the findings and events of parathyroidectomy.

Insufficient

Immediate Postoperative Issues

The immediate clinical issues after parathyroidectomy include hematoma and bone hunger/transient hypoparathyroidism and are covered in this Section. The long-term complications of parathyroidectomy include operative failure (persistent or recurrent pHPT, Section 15), RLN injury, and hypoparathyroidism (Section 16).

Surveillance for Hematoma

Neck hematoma is a potentially life-threatening complication. Much of the literature focuses on post-thyroidectomy hematoma rates because the incidence is thought to be even lower after parathyroidectomy than thyroidectomy. The rate of hematoma after parathyroidectomy is typically on the order of 0.3%.^{444,593,594} Multiple retrospective series have found no re-explorations for symptomatic hematoma after MIP.⁵⁹³⁻⁵⁹⁹

Predicting which patient will develop a postoperative hematoma is difficult. A large retrospective case-matched control study found no perioperative risk factors for compressive hematoma after cervical endocrine surgery.⁵⁹³ However, certain factors such as coagulopathy, need for anti-coagulation, and hemodialysis, among others, are anecdotally thought to be associated with a higher risk of hematoma and should be considered by the surgeon. Aside from prevention through meticulous surgical technique, early recognition is the key to the safe and successful management. The committee reached strong consensus that following parathyroidectomy patients should be observed in a monitored setting for signs and symptoms of hematoma and that, if at all possible prior to discharge, a member of the surgical team should evaluate patients for its potential presence. The time period of observation for hematoma depends on the individual surgeon's practice and experience. In an early large series, 60% of hematomas were discovered after 6 hours of observation, suggesting that an overnight stay was indicated.⁵⁹³ However, numerous later large single institution series found that even in the case of BE, virtually all cervical hematomas were discovered within 4-6 hours postoperatively.^{40,264,444,600,601} The length of observation is dependent on the individual surgeon's practice.

Classic signs and symptoms of a postoperative neck hematoma include progressive swelling, neck pain or pressure, dysphagia, changes in voice quality, a feeling of impending doom, and respiratory distress. If present, a hematoma requires emergent evacuation. The surgeon's judgment is paramount in determining if a hematoma is developing. While ultrasound may be an adjunct, it is by no means universally used and may also delay necessary emergent care.

Management of Hematoma

Although the reported incidence of symptomatic hematoma after parathyroidectomy is consistently <1%, it is a potentially life-threatening complication.^{444,593,602} Objective literature is surprisingly scant however

the committee reached strong consensus on the following management principles. When hematoma is diagnosed, if the patient is stable, there is no immediate concern for the airway, and an operating room is available, the safest course of action is to immediately evacuate the hematoma in the operating room with appropriate anesthesia support. It is important to note that once the patient is supine, they may develop sudden onset or worsened respiratory distress, and emergent intubation may be required. If a hematoma is causing immediate life-threatening respiratory distress, emergent evacuation should be performed at the bedside, followed by intubation and intraoperative surgical management.⁶⁰³

- **RECOMMENDATION 14-2:** After parathyroidectomy, patients should be observed in a monitored setting for the development of cervical hematoma. Evidence of compressive hematoma after parathyroidectomy should prompt emergent decompression.

Strong Recommendation - Low quality evidence

Hypocalcemia

After parathyroidectomy the reported rates of moderate postoperative hypocalcemia range from 5-47%. Although a common occurrence especially in vitamin D deficient patients or those with malabsorption for any reason (e.g. celiac disease or prior bariatric surgery), symptomatic hypocalcemia is typically transient and can usually be managed as an outpatient.^{444,446,604-607} Patients undergoing BE have a significant higher rate of both mild and severe hypocalcemic symptoms and have lower postoperative calcium levels than in MIP.^{40,608}

Over the years, many strategies have been employed to address the potential for postoperative relative hypocalcemia and/or symptomatic hypocalcemia. The abundance of strategies is to some degree compounded by varying definitions. After parathyroidectomy, patients can have transient paresthesias in association with low or normal calcium levels, but hypocalcemia can also be asymptomatic, moreover different laboratories define hypocalcemia differently. Strategies for helping patients avoid or resolve paresthesias after parathyroidectomy using prophylactic calcium supplementation may be based on a variety of parameters such as preoperative calcium level, adenoma weight, rate of drop of IPM levels, or immediate or 24 hour calcium levels.^{444,446,596,604-607,609-615} In a recent survey of endocrine surgery fellowship training programs in North America, 68%

discharge patients on prophylactic calcium supplementation while 16% prescribe it selectively.⁹⁸ A typical postoperative regimen appears below (Rec 14-6).

After initial parathyroid surgery, the rate of permanent hypoparathyroidism is exceedingly low (0-3.6%; Section 16).^{444,446,606,608,611} Severe or prolonged postoperative hypocalcemia requiring intravenous calcium administration is quite rare after initial parathyroidectomy but may complicate reoperation (Section 17).

- **RECOMMENDATION 14-3:** Short-term calcium and/or vitamin D supplementation for prophylaxis against hypocalcemia should be considered following parathyroidectomy.

Weak Recommendation - Low quality evidence

Discharge Timing

When to allow patients to leave the hospital after parathyroid surgery depends on the individual surgeon's practice environment and experience. The major concerns about outpatient parathyroidectomy are potential for symptomatic hypocalcemia, which is common but typically self-limited, and life-threatening hematoma which is rare.

Most patients with hypocalcemic symptoms can be managed on an outpatient basis.⁴⁴⁶ A prospective randomized trial found that without prophylactic calcium supplementation, patients became most symptomatic and calcium levels declined at 24-48 hours after the operation vs. the immediate postoperative period.⁶⁰⁸ Most studies suggest that hypocalcemia typically does not develop until the third or fourth postoperative day.^{610,611} This finding underlines the concept that that overnight observation is not adequate for monitoring of hypocalcemia, as do the numerous studies reporting that post-parathyroidectomy neck hematoma is almost universally discovered by 4-6 hours postoperatively.^{40,264,444,600,601}

While an in-hospital overnight observation was the standard approach in decades past, a number of groups have published single institution results of outpatient parathyroidectomy and reported it to be safe in well-selected patients managed with observation for hematoma and an algorithmic strategy for addressing potential hypocalcemia.^{40,454,599,600,616} The specific safety of outpatient parathyroidectomy in the elderly has also been reported.²⁶⁴ The choice of outpatient vs. inpatient recovery appears to depend on the surgical

approach (BE vs. MIP), training, and volume of the surgeon. High-volume surgeons with endocrine surgery fellowship training and a preference for MIP choose outpatient parathyroidectomy more often.⁹³ Highlighting this trend, a survey of endocrine surgery fellowship training programs found that 89% offered outpatient surgery, with 47% discharging more than 90% of parathyroidectomy patients the same day.⁹⁸ However, an overnight stay after surgery for pHPT is also a reasonable strategy and in particular, may be appropriate for patients undergoing difficult surgery (e.g. reoperation, extensive exploration, subtotal parathyroidectomy with concern about remnant viability) or who have severe vitamin D deficiency, social issues, or are expected to be non-compliant.

- **RECOMMENDATION 14-4:** Outpatient parathyroid surgery can be considered in selected patients.

Weak Recommendation - Low quality evidence

Long-term Calcium Supplementation

As stated above there is no standard for whether or not patients receive prophylactic calcium supplementation in the immediate postoperative period to prevent or lessen symptoms of hypocalcemia. Some groups defer calcium supplements until the patient is symptomatic. Experts who routinely prescribe calcium postoperatively use disparate regimens that vary from 1-4 grams daily for a variable period of time.^{40,444,595,612}

Long-term calcium supplementation is a more straightforward issue. While no clear guidelines exist, most experts agree that patients should meet recommended daily intakes to help with bone remineralization (leading to the expected increase in BMD in the first year after parathyroidectomy) and maintenance of bone health. In 2010, the Institute of Medicine (IOM) assessed more than one thousand studies and reports in formulating the 2010 Dietary Reference Intakes for Calcium and Vitamin D in which it recommends the following calcium intake levels:

- Women 19-50: 1000mg daily
- Women >51: 1200mg daily
- Men 19-71: 1000mg daily
- Men >71: 1200mg daily⁶¹⁷

After parathyroidectomy, patients are typically supplemented with calcium carbonate since it is less expensive and requires fewer pills than calcium citrate. However, calcium citrate is preferred for patients who have undergone gastric bypass, are taking proton pump inhibitors, or otherwise have impaired gastric acid secretion or malabsorption syndromes. There are other benefits to long-term calcium supplementation; in a large retrospective study, patients who had curative parathyroidectomy were more likely to also have normal 6 month PTH levels when they received long-term postoperative calcium supplementation.⁶¹⁸

A typical postoperative regimen is 500 mg of elemental calcium (i.e. 1250 mg calcium carbonate) twice daily, increased as needed if specific paresthesias develop short-term, reduced 2-3 weeks after surgery, and continued together with replacement Vitamin D or a multivitamin for 6 months. Determination of long-term cure is addressed in Section 15.

- **RECOMMENDATION 14-5:** After apparently successful parathyroidectomy, calcium intake should follow the Institute of Medicine (IOM) Dietary Reference Intakes.

Strong Recommendation - Moderate quality evidence

Long-Term Vitamin D Supplementation

Vitamin D deficiency has been reported to exacerbate various medical issues, from worsening BMD to cardiovascular disease.^{619,620} In addition, after apparently successful parathyroidectomy, up to 40% of patients may have elevated PTH levels postoperatively which some have attributed at least in part to vitamin D deficiency (See Section 15: Cure and Failure).^{611,618,621,622} The combination of an elevated PTH level and low 25-OH vitamin D levels has been associated with a higher rate of fracture in postmenopausal women who are normocalcemic.^{623,624} Achieving normal vitamin D levels postoperatively may help improve BMD, absorption of calcium, and normalization of PTH levels.^{327,618,622,625} However, a national survey of endocrine surgery fellowship training programs found that in 2011, only 5% of programs routinely prescribe vitamin D supplementation and the rest do not prescribe vitamin D supplements or do so only selectively.⁹⁸

To facilitate absorption of calcium and maintenance of skeletal health, postoperatively, patients who are 25-OH vitamin D deficient should have their vitamin D levels supplemented by the surgeon or the

multidisciplinary care team to which he or she belongs, ideally to a “sufficient” level of 25-OH vitamin D, defined as >30ng/ml.³²⁶ Once patients have achieved a normal 25-OH vitamin D level, they should receive the recommended daily allowance for vitamin D intake. In 2010, the Institute of Medicine recommended the following vitamin D intake levels:

- Men and Women up to 71: 600 International Units
- Men and Women >71: 800 International Units⁶¹⁷
- **RECOMMENDATION 14-6:** Patients who are vitamin D deficient should receive vitamin D supplementation after apparently successful parathyroidectomy.

Strong Recommendation - Moderate quality evidence

Urgent Readmission

Urgent readmission after parathyroidectomy is rare. While hematoma and symptomatic hypocalcemia may lead to readmission, several large series have demonstrated that <1% of patients are re-admitted.^{40,444,593,599,600,616} In a review of the National Surgical Quality Improvement database, 3.8% of parathyroidectomies performed for primary, secondary and tertiary disease led to readmission within a 30-day period.⁶²⁶ This group found that declining functional status, pre-operative hemodialysis, increasing American Society of Anesthesiologists class, malnutrition, and unplanned re-operation were associated with a higher rate of readmission. Interestingly, early discharge (<24 hours) was associated with a lower readmission rate in this study.

Postoperative Visits

The timing of the first postoperative visit ranges from days to up to a month depending on the practice and resources of the individual surgeon. At that visit, laboratory testing should include a calcium level. If the calcium level is elevated it is rechecked after cessation of calcium supplementation, and if still elevated, an evaluation for operative failure is begun (Section 15). Patients should also be assessed for potential improvement of preoperative signs and symptoms, incisional healing, paresthesias, hypocalcemia, and voice quality (Section 16).

In a national survey of practice patterns, at least 40% of surgeons performing parathyroidectomy leave the follow-up to the referring physician.⁹³ However, the definition of successful parathyroidectomy is normocalcemia at 6 months and determining the outcomes of potential surgical complications (e.g. permanent hypoparathyroidism, permanent RLN injury) also requires evaluation for at least 6 months (Sections 15 and 16). Therefore, in order to ensure that surgeons are knowledgeable of their own outcomes, the committee reached strong consensus that it is the responsibility of the surgeon individually or in conjunction with their multidisciplinary care team to track the progress of patients at least until the 6-month postoperative mark is reached, i.e. to ensure that adequate follow-up is available and to conduct or oversee that follow-up as necessary. Whether this monitoring is done in the form of an in-person visit, phone call, and/or lab check, depends on the practice pattern of the individual surgeon, the compliance of the patient and other factors. At 6 months, laboratory testing should include calcium, PTH, and 25-OH vitamin D levels. If there is evidence of persistent pHPT, patients should be considered for reoperative parathyroidectomy (Section 17). Patients should also be re-assessed for voice quality, evidence of hypocalcemia, and incisional healing.

- **RECOMMENDATION 14-7:** At 6 months, surgeons individually or in conjunction with the multidisciplinary care team should assess post-parathyroidectomy patients for cure and evidence of long-term complications.

Strong Recommendation - Low quality evidence

15. CURE AND FAILURE

Cure of Primary Hyperparathyroidism

Definitive cure for primary hyperparathyroidism is achieved by surgical resection of abnormal and hyperfunctional parathyroid tissue.⁴⁴⁶ The goal of surgery is biochemical cure defined as durable normocalcemia. Cure rates for parathyroidectomy in sporadic pHPT should approach 95-99%. In part because initial and immediate postoperative fluid changes can misleadingly mimic true eucalcemia, the 6 month time point is the long-established interval for confirming cure, and for defining failure as persistent or recurrent disease.^{239,627-630}

Although normalization of PTH levels is also desirable, it is not a required component to define cure. There is no role for the routine measurement of PTH in the normocalcemic patient in the immediate postoperative period. Multiple studies spanning the eras of routine BE and MIP have shown that postoperative PTH can be elevated for weeks to months in up to 40% of patients^{618,631-634}. Etiologies for persistent elevation of PTH in the setting of a postoperative normal serum calcium include: vitamin D deficiency^{618,632}, mild renal insufficiency^{633,634}, compensatory, i.e. hyperfunction of previously suppressed normal glands⁶³⁵, unrecognized FHH, and increased mineralization of bone (when severe, this is referred to as hungry bone syndrome and may be associated with hypocalcemia as well as elevated bone formation markers, such as PO₄)^{634,636-638}. However, because non-normalization of PTH can also be an indicator of failure due to persistent or recurrent disease^{618,630,633,637,639} the committee reached strong consensus that such patients should be followed with repeat biochemical evaluations annually.

- **RECOMMENDATION 15-1:**

- a) Cure after parathyroidectomy is defined as the reestablishment of normal calcium homeostasis lasting a minimum of 6 months.

- Strong Recommendation - High quality evidence**

- b) Patients with normocalcemic pHPT who have persistently elevated PTH after parathyroidectomy should be evaluated and treated for causes of secondary HPT and if none are present, monitored for recurrent disease.

- Strong Recommendation - Low quality evidence**

While it is not used to define cure, the IPM response can help to predict operative success (Section 6). During MIP utilizing a validated IPM protocol, if the protocol's specific criteria are met to suggest adequate resection of all hyperfunctional tissue, success is predicted with high cure rates: 97-99.8%^{239,356,376,640-642}. However, false positive decreases in IPM do occur (Section 6). Moreover, since the implementation of IPM in the 1990's there has been increasing recognition that in patients found to have MGD during the course of exploration, surgical failure may also be predicted by an incomplete IPM drop^{362,377,643-645} such as a drop to <65

but >40 pg/mL (Section 6). IPM kinetic analysis may also help to predict cure^{374,390-394}, and is reported to decrease the rate of missed MGD producing an additional 1% lower risk of long term recurrence³⁵⁹.

Despite varying surgical techniques and IPM protocols, with appropriate surgical judgment and experience, long-term cure rates for initial parathyroidectomy are 95-99.8% for sporadic pHPT^{96,239,356,376,451,629-631,640-642,646-649}. The ability to recognize abnormal glands intraoperatively may also impact long term cure or failure, for example a recent study reports that a first resected gland weight of <200 mg may predict an increased risk of failure³⁵⁵.

RECOMMENDATION 15-2 : Surgeons should choose an operative approach that in their hands carries a high cure rate, low risk profile, and comparable cost to other available techniques.

Strong Recommendation - Low quality evidence

Cure of Normocalcemic pHPT

The condition of normocalcemic pHPT requires additional consideration to establish surgical cure (Section 1). In this setting a determination of enduring postoperative calcium levels in the normal range lacks definitive meaning since calcium levels were normal preoperatively⁶⁴⁴. As in hypercalcemic disease, in normocalcemic pHPT if parathyroidectomy is determined to be appropriate and necessary, the response of IPM may help to identify MGD²⁵. To date, the data on surgical cure rate remain unclear due to small study size, difficulties in definition of normocalcemic pHPT, and lack of long-term follow-up^{362,650-652}; to this end, further studies exploring outcomes in patients with presumed normocalcemic pHPT are necessary.

- **RECOMMENDATION 15-3:** In normocalcemic pHPT, the definition of cure must include normal calcium and PTH levels >6 months after surgery.

Insufficient

Cure in Familial pHPT

In patients with a genetic disorder which leads to pHPT (MEN1, MEN2, MEN4, HPT-JT and FIHPT), a different endpoint of care pertains. In this unique group, which has inherent MGD, lifelong cure may not

possible and the goal of surgery is better defined as an extended time to recurrence; in such patients it is not a matter of if they will recur, but when. For example, in MEN1 a serum growth factor (FMEN-1 mitogen) is reported to stimulate parathyroid gland growth⁶⁵³. The surgical goal in hereditary HPT is to achieve normal calcium homeostasis sufficient to allow the patient to live with the disease but without complications from the disease or its surgical management^{397,474} (Section 9). With sound surgical judgment and technique, durable cure rates can be as high as 80-98% for familial disease overall, varying by type of operation and etiology, with recurrence rates of 15-20% in HPT-JT^{481,482}, 17-46% in MEN1^{61,62,483,654}, 6-11% in MEN2^{474,476,477} and 11% in FIHPT⁶⁵⁵. In general, it is reasonable to expect a normocalcemic interval of 5-15 years before recurrence in genetically related pHPT⁶⁵⁶.

Failure after Parathyroidectomy for pHPT

Operative failure remains the most common complication of parathyroid surgery. Failed initial parathyroid surgery carries higher costs and reoperative risks (Section 17) and is classified into either persistent or recurrent disease. In the literature for decades, persistent pHPT is defined by hypercalcemia that is present within the first 6 months after surgical intervention.^{239,304,361,415,628,630,639,657-659} Recurrent disease is the re-elevation of serum calcium level >6 months after parathyroidectomy^{417,452,453,660-662}. Diagnosis of either condition requires the absence of exogenous calcium administration and the exclusion of causes of secondary hyperparathyroidism.

The first step in determining operative success or failure is postoperative serum calcium assessment at the initial postoperative visit. If hypercalcemia is present, its causes can include excessive oral calcium or vitamin D supplementation, prolonged tourniquet time, error in original diagnosis of pHPT, FHH, or residual hyperfunctional parathyroid tissue. These causes should be considered and addressed. For example, if the serum calcium level is elevated in the setting of calcium supplementation, this should be withheld and laboratory assessment repeated. As previously noted (Recommendation 15-1) there are no data to support routine measurement of PTH in the early postoperative period in eucalcemic patients. Early postoperative PTH elevation is common^{618,630-635,639}, and may be an appropriate response to reach balanced homeostasis after

curative surgery. It may also reflect transient hypocalcemia, bone hunger, insufficient calcium intake, and renal disease.

- **RECOMMENDATION 15-4:** Persistent pHPT should be defined as a failure to achieve normocalcemia within 6 months of parathyroidectomy. Recurrent pHPT is defined by recurrence of hypercalcemia after a normocalcemic interval at >6 months after parathyroidectomy.

Strong Recommendation – High quality evidence

Causes of Persistent and Recurrent pHPT

In evaluating persistent pHPT, several possible causes should be considered. Although sources of initial error in diagnosis include unrecognized FHH, secondary HPT, severe vitamin D deficiency, and misclassification of hypercalcemia of malignancy as pHPT (in this scenario PTH is usually low), the most common reason for persistent pHPT after initial parathyroidectomy is an unresected hyperfunctioning gland, whether from a missed adenoma or unrecognized MGD. This situation may be driven by a lack of surgical expertise^{256,663-665}. To avoid a missed hyperfunctioning gland, the surgeon needs the expertise to conduct a detailed, thorough cervical exploration (Section 8)^{102,666-670}. In addition, surgeons whose exploration is guided by preoperative imaging must realize the limitations of these radiographic studies and be prepared to do additional dissection at the initial surgery if the preoperatively identified location is incorrect. Likewise surgeons who utilize IPM must be able to continue with an organized algorithmic exploration for MGD if removal of one or more abnormal parathyroid glands does not produce an appropriate response (Section 6).

Causes of recurrent pHPT include untreated or interval development of MGD, remnant hypertrophy, parathyroid carcinoma or metastasis⁶⁷¹⁻⁶⁷³, graft hyperplasia, revascularization of a previously devascularized *in situ* hyperfunctioning gland, and parathyromatosis resulting from capsular fracture of a gland during initial excision⁶⁷⁴⁻⁶⁷⁶. In genetically determined pHPT, such as MEN1 there are accepted and expected rates of recurrence (Section 9).

An essential concept for surgical success is that to reduce the chance of failure, each surgeon must be cognizant of his/her own success and failure rates, utilizing all available information both preoperatively

(patient and family history, laboratory results and imaging) and intraoperatively (results of IPM and other adjuncts) together with clinical judgment. By learning in this way, repeated issues may be avoided. The results of personal safety and quality can be recorded and analyzed individually or by available online collaborative group programs⁶⁷⁶.

16. MANAGEMENT OF OTHER COMPLICATIONS

Recurrent Laryngeal Nerve Injury

Vocal fold immobility can result in undesirable voice limitations, breathing complaints, aspiration, dysphagia, and a diminished quality of life.¹³ Vocal cord immobility can be caused by thermal, blunt, sharp, or traction injuries to the RLN during parathyroid surgery. The superior and inferior parathyroid glands reside posterolateral and anteromedial to the RLN, respectively. Familiarity with the anatomic relationships (Section 2) and use of gentle dissection and careful retraction are required to minimize the risk of RLN injury during parathyroid exploration and resection. Parathyroid tumors may be adjacent or adherent to the RLN, which is then especially susceptible to injury. PCA can invade or surround the RLN and in some cases with local extension, gross clearance of PCA can even require resection of a segment of the RLN (Section 12 and below). Intubation itself can cause local trauma and rarely, arytenoid dislocation.

Postoperative voice complaints after parathyroidectomy may be a consequence of vocal fold edema or contusion, laryngeal inflammation, or RLN injury. The local effects of intubation generally wear off promptly, but aspiration or persistent hoarseness after parathyroidectomy should prompt clinicians to consider formal evaluation by fiberoptic laryngoscopy or transcutaneous laryngeal ultrasound to exclude vocal fold dysfunction.^{54,340,677}

Although the rate of permanent RLN injury is quite low for initial parathyroidectomy, groups that perform routine laryngoscopy after reoperation report higher rates ranging from 7-9%.⁶⁷⁸ In contrast, surgeons who do not perform routine laryngoscopy report RLN injury rates as low as 0.4% after reoperative parathyroidectomy.⁶⁷⁹ Patients diagnosed with RLN dysfunction or objective symptoms of aspiration should

undergo evaluation and potential intervention by a clinician experienced in the management of voice abnormalities.

Operative RLN transection results in irreversible vocal fold paralysis, the eventual treatment of which can include intracordal injection, thyroplasty, arytenoid adduction, or reinnervation. Common RLN reinnervation techniques include direct neurotomy or ansa cervicalis to RLN anastomosis. Although laryngeal reinnervation does not restore normal movement, it promotes the long-term maintenance of vocal fold bulk, tension, and a medialized position. In contrast to delayed interventions for vocal fold paralysis, which cannot prevent laryngeal muscle atrophy, immediate reinnervation can be done at the time of a recognized RLN injury with good long-term outcomes measured by subjective and objective voice parameters.^{45,680} Even in cases when primary repair cannot be accomplished, reinnervation of the adductor muscles can be achieved using the ansa cervicalis nerve at the initial surgery, or in a delayed fashion.⁴⁵ When RLN injury is suspected but the nerve is anatomically intact, reinnervation should not be attempted.

- **RECOMMENDATION 16-1:** When RLN transection is recognized during parathyroidectomy, a reinnervation procedure should be attempted.

Strong Recommendation - Low quality evidence

Hypoparathyroidism

As described in Section 14, typical early symptoms of postoperative hypocalcemia, can include perioral numbness and fingertip paresthesias and may be a consequence of either hypoparathyroidism or euparathyroid bone hunger. Within days of surgery, however, severe postoperative hypocalcemia may go on to result in tetany, muscle cramping, and even cardiac arrhythmia.

Transient hypoparathyroidism is common after thyroid surgery, with reported rates as high as 46% in patients with concurrent thyrotoxicosis⁶⁸¹, and diagnosis includes documentation of an elevated phosphorus level. Parathyroid gland “stunning” with transient impairment of function can occur after manipulation, dissection or biopsy of parathyroid glands and such patients may require calcium and even calcitriol administration to avoid transient symptomatic hypocalcemia (Section 14). Calcitriol enhances calcium

absorption in the gut, and its effect on serum calcium begins to be seen approximately 36 hours after the medication is started. In transient hypoparathyroidism, both calcitriol and oral calcium supplements should be weaned as soon as tolerated since they negatively regulate parathyroid function and may impair recovery.⁶⁸²⁻⁶⁸⁴

In contrast, prolonged hypoparathyroidism is a chronic condition characterized and often defined by such diminished parathyroid function that ongoing calcitriol treatment is required for at least 6 months after surgery; recently the American Association of Clinical Endocrinologists and American College of Endocrinopathy defined temporary (transient) hypoparathyroidism as hypocalcemia requiring a medical regimen for >12 months following cervical surgery.⁶⁸⁵ The treatment of prolonged hypoparathyroidism requires long-term biochemical monitoring to avoid complications of hypercalcemia, which include nephrolithiasis, nephrocalcinosis, renal insufficiency, soft tissue calcification, cataracts, depression and basal ganglia calcification.^{23,686,687} Treatment with exogenous recombinant human PTH (1-84) is an FDA-approved therapy that can also improve hypocalcemia and may enable recovery of parathyroid hormone secretion in patients with prolonged hypoparathyroidism, although the mechanism of this delayed recovery is as yet poorly understood.^{25,688,689}

- **RECOMMENDATION 16-2:** Patients with transient hypoparathyroidism after surgery should be treated with calcium and, if necessary, calcitriol supplements, which should be weaned as tolerated. Patients with prolonged hypoparathyroidism may be considered for recombinant PTH therapy.

Weak Recommendation - Low quality evidence

Other Complications

Other rare complications that surgeons should be aware of include infection, dysphagia, pain syndromes, pneumothorax, superior laryngeal nerve dysfunction, Horner's syndrome, lymphatic leak, postoperative hyperthyroidism, pseudogout, pharyngeal perforation from anesthetic probe placement, allergic reaction to OR medications and suture material, and intraoperative cardiovascular events.

17. REOPERATION

In patients with persistent or recurrent pHPT, reoperative parathyroid surgery may be required to achieve biochemical cure and is recommended. However, any operation in which the cervical region has been manipulated increases the risks of morbidity during subsequent surgery, including injury to the recurrent laryngeal nerves and devascularization of otherwise normal parathyroid glands.⁵⁸⁷ Therefore, the term ‘reoperation’ is defined here as parathyroid exploration after any previous cervical exploration, including but not limited to previous parathyroidectomy, thyroidectomy, cervical fusion via an anterior approach, tracheostomy, thoracic surgery, and carotid endarterectomy. A careful assessment to confirm the diagnosis, establish if an indication for reoperation is present, and evaluate the results of preoperative imaging should be performed prior to reoperation (Figure 2).

Preoperative Evaluation of Persistent/Recurrent pHPT

Confirmation of the Diagnosis

In patients presenting with suspected persistent or recurrent disease (Section 15) it is first critical to formally confirm the diagnosis of pHPT (Section 1). This includes a thorough review of all biochemical data both after and before the failed operation, review of medications that can alter calcium metabolism (e.g. lithium, thiazide diuretics), consideration of alternative causes of PTH elevation (e.g. renal insufficiency, renal calcium leak, FHH, vitamin D deficiency), and taking a detailed history for familial disease that would place patients at risk for persistent or recurrent pHPT (Section 9). The possibility of PCA and/or parathyromatosis must also be considered.

Stricter Indications for Reoperation

Reoperative parathyroidectomy can be challenging given tissue fibrosis, distortion of normal anatomy, and obliteration of normal dissection planes by scar. Reported cure rates in reoperation range from 82–98%, which is lower than for patients undergoing initial parathyroidectomy.^{247,249,315,452,468,587,678,690-694} Higher rates of postoperative hypoparathyroidism and recurrent laryngeal nerve injury also occur with reoperation, at 5-8% and up to 15% respectively, particularly in patients who underwent BE at the initial procedure.^{95,246,247,587,678,693-695} As a result, there is generally a higher threshold to indicate reoperation and many experts require substantial

disease features to be present, such as significant symptomatology, nephrolithiasis, osteoporosis, hypercalciuria or a documented decrease in renal function, before recommending reoperation for persistent or recurrent pHPT.^{249,315,452,468,587,690}

Review of Existing Data

In addition to confirmation of the diagnosis, every effort should be made to obtain the previous imaging, the operative and pathology reports, and the pathology slides, if available. Salient information that can be obtained from operative reports may include prior intraoperative identification and assessment of parathyroid glands, the extent of exploration, breach of the parathyroid capsule, and the incidental finding of histologic parathyroid tissue in a thyroidectomy specimen. Information from other cervical operations such as carotid endarterectomy, anterior cervical discectomy or thyroidectomy may also provide information for planning parathyroidectomy in a reoperative field including highlighting the need for vocal cord examination preoperatively. Pathology reports can also provide information regarding the weight and size of previously resected parathyroid glands, as there is some data to suggest that smaller parathyroid glands may be associated with MGD.^{235,441} Pathology data may also document prior resection of non-parathyroid tissue such as thyroid nodules, lymph nodes or thymic tissue and indicate prior extent of dissection. Prior imaging records may help ascertain the location of a “missed” parathyroid adenoma in persistent disease. A re-review of the family history is also important, as time may have allowed for the discovery of non-PTH-mediated hypercalcemia, such as FHH. The family history may also lead to the identification of previously unrecognized MEN1 kindred, which can change the operative approach. Patients undergoing parathyroid reoperation also need formal assessment of RLN function preoperatively.

Imaging

In contrast to initial surgery, positive preoperative imaging is essential in planning reoperative parathyroidectomy, as abnormal parathyroid glands may be in eutopic or ectopic locations (Figure 1) and as reoperation will often be conducted through scar. Most experienced parathyroid surgeons require at least 1 positive imaging study prior to reoperation, and some require 2 concordantly positive studies.^{254,452,468,587,670,690-}

^{693,696} In one study, the reoperative failure rate was 4 times higher in patients who had nonlocalizing imaging.⁶⁹⁷

Reoperative imaging (Section 4) can include anatomical (ultrasound, 4D-CT) and functional (sestamibi ± SPECT, 4D-CT, selective venous sampling) studies. In a recent report, 4D-CT had higher sensitivity (88%) than sestamibi imaging (54%) in reoperation.³⁰⁸ In a study of 90 patients undergoing reoperation there was a 90% concordance rate between 4D-CT and surgical findings compared to a 63% concordance rate between imaging and surgical findings prior to use of 4D-CT.⁶⁹⁸

It is essential for the managing team to realize that just because an abnormal gland is identified on imaging, does not mean that it is an adenoma or that it represents the only abnormal parathyroid gland. Nonoperative management of persistent or recurrent pHPT is generally pursued in patients with mild disease and/or non-localizing imaging studies.

While noninvasive imaging modalities are much preferred, invasive techniques do play a selective role.^{468,488,587,690,691} Invasive studies should not be performed in place of noninvasive imaging and should be done at a high-volume center (Section 4). Again, in contrast to initial surgery, preoperative US-guided fine needle aspiration of suspected abnormal parathyroid glands may be useful.^{294,551} Such aspirate samples should be sent for both cytology (primarily to rule out other diagnoses) and for PTH level; in one study an elevated PTH washout level, defined as greater than the serum PTH level, had a positive predictive value of 100%.⁴⁸⁸ However, given the risks of hematoma, parathyromatosis, histologic distortion, and cancer seeding, FNA should be limited to select reoperative patients in whom noninvasive imaging has failed.

Selective venous sampling (SVS) can be utilized for reoperative localization of hyperfunctional parathyroid tissue; its use is rare and the technique is not possible for patients with previous cervical surgery in which thyroid and parathyroid vessels have been ligated. During SVS a catheter is placed in the femoral vein, allowing cervical and mediastinal venous blood to be assayed for PTH; detection of a gradient suggests lateralization of a target gland. SVS can be performed in conjunction with angiography, as increased vascularity of an adenoma may manifest by a localizing blush. In persistent/recurrent pHPT, SVS had an overall sensitivity of 83.3% (79.5% for single adenomas and 91.6% for hyperplastic glands).⁶⁹⁹ Alternative venous sampling techniques involving a systemic hypocalcemic challenge or concurrent 4D-CT, have shown excellent

localization rates as well. However, all SVS techniques are expensive, require significant technical and high-volume expertise, and can be associated with groin hematoma and vascular injury.^{690,691,699-701}

- **RECOMMENDATION 17-1:** The evaluation of persistent or recurrent pHPT should include confirmation of biochemical diagnosis, assessment of indications for surgery, review of prior records if available, and evaluation of RLN function.

Strong Recommendation - Low quality evidence

- **RECOMMENDATION 17-2:** Patients with persistent or recurrent pHPT should be evaluated by an experienced parathyroid surgeon prior to the decision to proceed with surgery or nonoperative management.

Strong Recommendation – Low quality evidence

Operative Approach

Prior to reoperative parathyroidectomy, there should be anticipation of whether single or multigland disease is likely present and what normal parathyroid tissue likely remains *in situ*. The imaged location(s) of abnormal gland(s) should be reviewed. Most residual parathyroid disease will be accessible via a cervical incision, but previous surgery may result in dense adhesions (e.g. between the strap muscles and underlying thyroid) making an anterior approach more difficult. . For example, the lateral approach in which a target superior gland in the tracheoesophageal groove and/or retroesophageal space is approached via the plane between the strap muscles and sternocleidomastoid muscle, may helpfully avoid scar tissue. When the target gland is thought to be inferior to the thyroid lobe, the thyrothymic approach, in which the infrahyoid muscles are divided as inferiorly as possible to allow direct access to the thyrothymic ligament, has been described.⁶⁷⁰ Even in reoperation, mediastinal parathyroid glands are typically accessible via a cervical incision, as the majority lie within the thyrothymic ligament or anterior mediastinum and can be gently pulled up and removed via cervical thymectomy; a cervical approach can often be utilized for parathyroid glands located <6 cm below the superior aspect of the head of the clavicle.⁷⁰² For patients with a missed superior adenoma in the middle

mediastinum, especially the aortopulmonary window, a transthoracic approach may be required, either via sternotomy or video-assisted thoracic surgery.^{696,703}

In patients for whom BE during reoperative parathyroidectomy may be required, the approach may be similar to initial parathyroidectomy (Section 8) but experts often prefer to stage the laterality of reoperation so as not to put both recurrent laryngeal nerves at risk during the same procedure, although this point is not yet well-reported in the literature.

Intraoperative Adjuncts in Reoperation

In addition to IPM (Section 6), which can also provide useful information for immediate postoperative management,^{692,693} other intraoperative adjuncts (Section 10) are often employed in reoperative parathyroidectomy.⁷⁰⁴⁻⁷⁰⁶ In a comparison of patients who underwent reoperative parathyroidectomy with or without IPM, 74% of those who did not have IPM were normocalcemic postoperatively, compared to 94% with IPM.⁶⁹³ Radioguidance has also been described for reoperation.^{707,708} Preoperative needle localization of suspected abnormal parathyroid glands is discussed above⁷⁰⁴⁻⁷⁰⁶. Other adjuncts described to be helpful in small institutional series include ultrasound-guided injection of methylene blue, recurrent laryngeal nerve monitoring, parathyroid autotransplantation and cryopreservation (Section 13). In particular, autotransplantation and/or cryopreservation should be considered if the target gland(s) is/are possibly the last remaining viable parathyroid tissue.

- **RECOMMENDATION 17-3:** IPM should be considered in patients undergoing reoperative parathyroidectomy for pHPT.

Strong Recommendation – Low quality evidence

CONCLUSIONS

Because the surgical treatment of pHPT has undergone extensive change in the last 2 decades, the AAES determined the need to develop evidence-based clinical guidelines to enhance the safe, definitive treatment of pHPT. These evidence-based guidelines provide a broad-based approach to the clinical spectrum of pHPT and, although they do not represent the only acceptable approach, serve as a sound template for the effective surgical management of pHPT to achieve cure as safely as possible.

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eTable 1. Table of Contents: The American Association of Endocrine Surgeons (AAES) Guidelines for Definitive Management of Primary Hyperparathyroidism

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eTable 2. Common Secondary Causes of Elevated PTH Levels

Cause	Comment
Chronic kidney disease	Creatinine clearance <60 ml/min
Medications (calcium normal or high)	Thiazide and loop diuretics, lithium
Medications (calcium normal or low)	Foscarnet, citrate (banked blood/plasma), EDTA, bisphosphonates, denosumab, cisplatin
Hypercalciuria secondary to renal leak	Renal hypercalciuria
Malabsorption syndromes	Celiac disease, inflammatory bowel disease, gastric bypass surgery, cystic fibrosis
Vitamin D (25-OH) deficiency/insufficiency	Deficiency commonly defined as <20 µg/L Insufficiency commonly defined as 20-30 µg/L

eTable 3. Selected Results of the Two Most Commonly Utilized IPM Protocols

Cure Criteria	Timing of PTH samples in the operating room	Usual # of PTH samples	Cure rates	Recurrence Rates (mean follow-up in months)
Miami: >50% PTH decrease at 10 minutes from the highest level, either pre-incision or pre-excision	1-Pre-incision: before incision 2-Pre-excision: before the blood supply to the gland is ligated 3-Five minute level: 5 minutes after gland removal 4-Ten minute level: 10 minutes after gland removal 5-Other levels++	3 to 4	97-99%	3% (50) Irvin ³⁵⁴ 2% (48) Carneiro ³⁶⁵ 3% (83) Lew ³⁷⁶ 1.2% (13) Lee ³⁶¹ 2.4% (9*) Schneider ³⁵⁷ 2.9% (21) Rajaei ³⁶⁰ 0.4% (15) Udelsman ³⁵⁶
Dual: >50% PTH decrease from the pre-incision level plus final PTH into normal range	1-Pre-incision: before incision 2-Ten minute level: 10 minutes after gland removal 3-Other levels++	2	97-99%	0.4% (10) Hughes ³⁶³ 0.5% (21.6) Wharry ³⁵⁹ n/a (NFS) Heller ³⁷⁷ n/a (NFS) Richards ³⁵⁸ 3.2% (28*) Wachtel ³⁶²

*Denotes median follow-up; ++, see text for details; NFS, no follow-up specified

eTable 4. Parathyroid Carcinoma in Large Retrospective Series

Institution	Publication	Years	n
National Cancer Database Registry	1999 ⁵⁵⁶	1985-1995	286
Swedish Cancer Registry	1992 ⁵⁵²	NA	95
Massachusetts General Hospital	1973 ⁵⁵³	1930-1973	70
Mayo Clinic	1992 ^{554,700}	1920-1991	43
The Netherlands Cancer Registry	2011 ⁷⁰⁹	1989-2003	41
University of California San Francisco	2011 ²⁵⁵	1966-2009	37
MD Anderson	2004 ¹⁸¹	1980-2004	27
University of Sydney	2011 ⁷¹⁰	1958-2010	21
Padua	2013 ⁶⁷⁸	1987-2008	19
Princess Margaret Hospital	2013 ⁵⁵⁵	1976-2005	16
Lahey Clinic	1985 ⁷¹¹	1942-1984	9
Cleveland Clinic	1993 ^{704,712}	1938-1988	6