JAMA Surgery | Special Communication

The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism

Scott M. Wilhelm, MD; Tracy S. Wang, MD, MPH; Daniel T. Ruan, MD; James A. Lee, MD; Sylvia L. Asa, MD, PhD; Quan-Yang Duh, MD; Gerard M. Doherty, MD; Miguel F. Herrera, MD, PhD; Janice L. Pasieka, MD; Nancy D. Perrier, MD; Shonni J. Silverberg, MD; Carmen C. Solórzano, MD; Cord Sturgeon, MD; Mitchell E. Tublin, MD; Robert Udelsman, MD, MBA; Sally E. Carty, MD

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 review 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.

Invited Commentary page 969

Author Audio Interview at jamasurgery.com

Supplemental content at jamasurgery.com

CME Quiz at jamanetworkcme.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Scott M. Wilhelm, MD, Department of Surgery, University Hospitals/Case Medical Center, 11100 Euclid Ave, Cleveland, OH 44118 (scott.wilhelm@uhhospitals.org).

JAMA Surg. 2016;151(10):959-968. doi:10.1001/jamasurg.2016.2310
Published online August 10, 2016.

The surgical treatment of primary hyperparathyroidism (pHPT) has undergone extensive change in the past 2 decades. The presentation, diagnosis, and medical management have been previously addressed by an international workshop.[1-4] To meet the need for a detailed focus on operative management, the American Association of Endocrine Surgeons (AAES) developed evidence-based guidelines to delineate the safe and effective practice of parathyroidectomy to achieve definitive treatment.

Methods

A multidisciplinary panel of endocrinologists, pathologists, surgeons, and radiologists established PubMed search parameters for the worldwide medical literature from January 1, 1985, to July 1, 2015, using the National Library of Medicine Medical Subject Headings and keywords (*hyperparathyroidism, primary*; *parathyroid neoplasms*; and *hyperparathyroidism*) linked by boolean operators. The writing group adopted the American College of Physicians grading system for evidence-based guidelines,[5] which uses a validated scale to critically evaluate the strength and quality of the evidence. Recommendations are designated *strong* when benefits clearly outweigh risks and/or the recommendation should be applied to all or most patients without reservation, *weak* for equivalent risks or uncertainty, and *insufficient* when evidence is conflicting or of poor quality. Evidence quality is graded *high* for randomized clinical trials or overwhelming evidence, *moderate* for randomized clinical trials with significant limitations or large observational studies, and *low* for small observational or case studies.

In guidelines construction, the evidence was rigorously examined, recommendations were graded, and text was amended to achieve consensus. Feedback was sought from an independent group of nonauthor clinicians, the AAES membership, and other expert sources.

These guidelines present a process for the evaluation and surgical treatment of pHPT based on evidence at the time of writing. They do not represent the only approach to the management of adult pHPT and are not meant to replace an individual physician's judgment. Adherence to the guidelines is not mandatory, may require adaptation in practice settings with barriers to implementation, and does not constitute a legal standard of care. The writing group had complete independence from the AAES in the production of the evidence-based guidelines.

Recommendations

The full evidence statements supporting the recommendations appear in the eAppendix and eTable 1 in the Supplement. The Supplement also includes additional details, technical descriptions, discussions of controversy, and expert advice on the surgical management of pHPT.

Diagnosis and Evaluation

Primary hyperparathyroidism is a common disorder that arises from autonomous overproduction of parathyroid hormone (PTH) by abnormal parathyroid glands. The disease is characterized by the persistent elevation of total serum calcium levels with corresponding elevated or inappropriately normal (ie, nonsuppressed) PTH levels. The diagnosis of pHPT is biochemical. The clinical presentation is heterogeneous, and the associated symptoms overlap with those of aging and disease. Patients with symptomatic pHPT have overt signs and symptoms; however, the definition of symptomatic disease is still evolving. Patients with asymptomatic pHPT have no disease-specific symptoms.

Normocalcemic pHPT is a recently recognized, incompletely characterized variant that presents with high PTH levels and normal total and ionized serum calcium levels. Some, but not all, patients may progress over time to hypercalcemic pHPT.[6]

Establishing the Diagnosis: Laboratory Testing

In pHPT, patients may occasionally have normal total and/or ionized calcium levels but are hypercalcemic most of the time. Thus, repeated measurements of calcium are required.[3] Total serum calcium levels are reported in milligrams per deciliter (to convert to millimoles per liter, multiply by 0.25) and should be corrected for serum albumin (eAppendix in the Supplement). Although pHPT and malignant tumors are the most common causes of hypercalcemia in adults, other causes should be considered. Patients with normocalcemic pHPT have normal serum and ionized calcium levels; thus, measurement of ionized calcium is necessary to establish the diagnosis of normocalcemic, but not hypercalcemic, pHPT.

In pHPT, PTH levels are high or inappropriately normal (ie, not suppressed despite hypercalcemia). Diagnosis of normocalcemic pHPT requires the exclusion of other causes of secondary elevation of PTH (eTable 2 in the Supplement). Nonparathyroid causes of hypercalcemia are associated with suppressed PTH. Renal function and vitamin D status should be assessed preoperatively.

- **Recommendation 1-1:** The biochemical evaluation of suspected pHPT should include serum total calcium, PTH, creatinine, and 25-hydroxyvitamin D levels (strong recommendation; moderate-quality evidence).

A 24-hour urinary calcium level is important to distinguish pHPT from familial hypocalciuric hypercalcemia, which is an autosomal dominant disorder of the renal calcium-sensing receptor that can mimic pHPT. Familial hypocalciuric hypercalcemia should be considered in patients with long-standing hypercalcemia, urinary calcium levels less than 100 mg/24 hours, and a calcium to creatinine clearance ratio less than 0.01 (eAppendix in the Supplement).

- **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).

Investigation of Symptoms, Features, and Complications

A careful history should be performed for objective renal and skeletal manifestations, including nephrolithiasis, fragility fractures, and osteoporosis. Subjective symptoms, including neuropsychiatric, cognitive, musculoskeletal, and gastrointestinal complaints (eAppendix in the Supplement), should be documented because parathyroidectomy may lead to improvement or resolution of these symptoms. Certain medications can cause biochemical changes that mimic pHPT (eAppendix in the Supplement). In 3% to 5% of patients,

pHPT occurs as a component of an inherited syndrome (eAppendix in the Supplement).[7-9]

- **Recommendation 1-3:** In patients with suspected pHPT, a personal and family history should be taken (strong recommendation; moderate-quality evidence).

Patients with otherwise asymptomatic pHPT may have nephrocalcinosis or silent nephrolithiasis; both are indications for parathyroidectomy.[4]

- **Recommendation 1-4:** In patients with asymptomatic pHPT, abdominal imaging should be performed for detection of nephrocalcinosis or nephrolithiasis (weak recommendation; low-quality evidence).

Primary hyperparathyroidism causes site-specific reduction in bone mineral density (BMD) and may predispose patients to fragility fractures.[4] Dual-energy x-ray absorptiometry (DXA) examination is appropriate for all patients with pHPT and should be performed to screen for clinically relevant skeletal manifestations.[4]

- **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).

In patients with pHPT attributable to a hereditary syndrome, the timing and extent of parathyroidectomy are affected by the presence and specific type of mutation present (eAppendix in the Supplement).[9]

- **Recommendation 1-6:** Genetic counseling should be performed for patients younger than 40 years with pHPT and multigland disease (MGD) and considered for those with a family history or syndromic manifestations (strong recommendation; low-quality evidence).

Epidemiology and Pathogenesis

The recognition of pHPT increased in the 1970s with automated routine calcium testing, and prevalence continues to increase today. Incidence appears to increase with age and is 2 to 3 times higher in women (eAppendix in the Supplement). Primary hyperparathyroidism remains underdiagnosed and undertreated.

Safe and effective parathyroidectomy requires mastery of the anatomical and pathophysiologic features of pHPT (eAppendix in the Supplement). Autonomous PTH secretion may be attributable to hyperfunction of 1 or more glands and is caused by 3 different pathologic conditions: adenoma, hyperplasia, or carcinoma. The overall frequency of MGD is 6% to 33% (eAppendix in the Supplement).

- **Recommendation 2-1:** Multigland disease affects approximately 15% of patients with pHPT and should be routinely considered in preoperative planning (strong recommendation; moderate-quality evidence).

Lithium-associated pHPT occurs in up to 15% of long-term users, with increased rates of MGD.[10] Molecular alterations also affect the pathophysiologic mechanisms and rates of MGD (eAppendix in the Supplement). Germline inactivating mutation of the *MEN1* gene (OMIM 613733) causes multiple endocrine neoplasia type 1, and somatic events occur in sporadic tumors; germline activating mutations of the *RET* (OMIM 188550) proto-oncogene result in multiple endocrine neoplasia type 2; the somatic *PRAD1* (OMIM 168461) rearrangement upregulates cyclin D1 in sporadic adenomas; and inactivating mutations of *CDC73* (formerly *HRPT2*) (OMIM 607393) occur as germline alterations in hyperparathyroidism–jaw tumor syndrome and familial isolated hyperparathyroidism and as somatic events in sporadic parathyroid cancer (PCA) (eAppendix in the Supplement).

- **Recommendation 2-2:** Exposure-related and genotype-phenotype correlations are predictive of parathyroid anatomical and pathophysiologic features and should be considered because they may affect the planning and conduct of surgery (strong recommendation; moderate-quality evidence).

Indications and Outcomes of Intervention

Parathyroidectomy is the only definitive treatment of pHPT. Symptomatic patients are expected to derive clear benefits from curative parathyroidectomy, and patients considered to be asymptomatic frequently report improvement in quality-of-life indexes.[11-14] Observation and pharmacologic therapy are less effective and less cost-effective than surgery, even when the patient is considered asymptomatic.[15] Long-term hypercalcemia should be avoided because of potential deleterious effects (eAppendix in the Supplement).[16-18] Referral to an experienced parathyroid surgeon is advised to determine whether the likelihood and benefits of cure outweigh the anticipated risks of the procedure.

- **Recommendation 3-1:** Parathyroidectomy is indicated, and is the preferred treatment, for all patients with symptomatic pHPT (strong recommendation; high-quality evidence).
- **Recommendation 3-2:** Parathyroidectomy is indicated when the serum calcium level is greater than 1 mg/dL above normal, regardless of whether objective symptoms are present or absent (strong recommendation; low-quality evidence).

After successful parathyroidectomy, the development of new kidney stones decreases markedly.[19] Although renal insufficiency and nephrocalcinosis do not resolve, surgery may prevent a further decline in the glomerular filtration rate (eAppendix in the Supplement).

- **Recommendation 3-3:** Parathyroidectomy is indicated for objective evidence of renal involvement, including silent nephrolithiasis on renal imaging, nephrocalcinosis, hypercalciuria (24-hour urine calcium level >400 mg/dL) with increased stone risk, or impaired renal function (glomerular filtration rate <60 mL/min) (weak recommendation; low-quality evidence).

Primary hyperparathyroidism causes a decrease in BMD, most pronounced at cortical bone sites, such as the distal third of the radius. Parathyroidectomy improves BMD and appears to reduce fracture rate, even for normal or osteopenic bone (eAppendix in the Supplement).[16]

- **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).

Patients 50 years or younger at diagnosis require prolonged monitoring and compared with older patients have a higher incidence of progression (eAppendix in the Supplement).[20]

- **Recommendation 3-5:** Parathyroidectomy is indicated when pHPT is diagnosed at 50 years or younger regardless of whether objective or subjective features are present or absent (strong recommendation; moderate-quality evidence).

The preoperative diagnosis of PCA may be difficult. If PCA is suspected, patients should be treated surgically because this is the only potentially curative treatment (eAppendix in the Supplement).

- **Recommendation 3-6:** Parathyroidectomy is indicated when the clinical or biochemical evidence is consistent with PCA (strong recommendation; high-quality evidence).

Patients who choose not to undergo surgery should undergo annual biochemical evaluation and periodic DXA. If the patient does not have the means or desire to adhere to a planned observation schedule, parathyroidectomy should be offered (eAppendix in the Supplement).[14]

- **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).

Patients with pHPT frequently have neurocognitive and neuropsychiatric symptoms. With varying response patterns, 3 randomized clinical trials demonstrated neurocognitive benefits of surgery vs observation.[13,14,21]

- **Recommendation 3-8:** Parathyroidectomy is recommended for patients with neurocognitive and/or neuropsychiatric symptoms that are attributable to pHPT (strong recommendation; low-quality evidence).

Patients with pHPT may have higher rates of myocardial infarction, hypertension, stroke, congestive heart failure, diabetes, and mortality (eAppendix in the Supplement). Observational studies in mild pHPT have yielded conflicting data about the improvement of cardiac parameters after parathyroidectomy. It is prudent to weigh 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).

Observational studies[16] suggest that several nontraditional and/or newly studied symptoms improve after successful parathyroidectomy, including muscle strength, functional capacity, gastroesophageal reflux, sleep patterns, and fibromyalgia (eAppendix in the Supplement).

- **Recommendation 3-10a:** The nontraditional 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 nontraditional features of gastroesophageal reflux and fibromyalgia symptoms may be considered in the decision for parathyroidectomy (insufficient evidence).

The success rate for surgeons who perform fewer than 10 parathyroidectomies per year is lower than for experienced surgeons (eAppendix in the Supplement). Volume of operations inversely correlates with complications, cost, and length of stay.[22]

- **Recommendation 3-11:** Parathyroidectomy should be conducted by surgeons with adequate training and experience in pHPT management (strong recommendation; moderate-quality evidence).

Although many pharmacologic agents have been used in an attempt to reduce the serum calcium level or stabilize BMD, none have improved both (eAppendix in the Supplement). In formal cost-effectiveness analyses, pharmacologic treatment is not optimal at any life expectancy.[15,23]

- **Recommendation 3-12:** Operative management is more effective and cost-effective than long-term observation or pharmacologic therapy (strong recommendation; moderate-quality evidence).

Parathyroidectomy for pHPT is not recommended when the risks of surgery or anesthesia are outweighed by the anticipated benefits of cure, as with severe or overriding medical illness (eAppendix in the Supplement). In patients who meet none of these indications for surgical intervention, refuse surgery, or are considered prohibitively high risk, medical intervention aimed at mitigating specific sequelae should be used.[2] For many patients, mild disease will progress over time.[24]

Parathyroid Localization Modalities: What Imaging to Perform and When

Guiding Principles

1. Imaging has no utility in confirming or excluding the diagnosis of pHPT.
2. Imaging results should not be used to select patients for surgical referral. Patients with negative imaging results remain candidates for parathyroidectomy.
3. There is marked regional variability in imaging accuracy. When imaging with initially negative results is performed again at high-volume centers, the sensitivity of localization improves to as high as 92%.[25]
4. Imaging is performed after deciding to proceed with parathyroidectomy and is performed for operative planning.
5. Parathyroid imaging is significantly less accurate for MGD.[26]
6. **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).
7. **Recommendation 4-2:** Patients who are candidates for surgery and have negative or discordant imaging results should still be referred to a parathyroid surgeon for evaluation (strong recommendation; low-quality evidence).

Cervical ultrasonography performed by an experienced parathyroid sonographer is the least costly imaging modality and, when combined with sestamibi or 4-dimensional computed tomography, is the most cost-effective strategy (eAppendix in the Supplement).[26-28] Preoperative ultrasound-directed fine-needle aspiration biopsy of parathyroid lesions is highly specific but is rarely necessary and can have undesirable consequences (eAppendix in the Supplement).

- **Recommendation 4-3:** Cervical ultrasonography is recommended to localize parathyroid disease and assess for concomitant thyroid disease (strong recommendation; low-quality evidence).
- **Recommendation 4-4:** Preoperative parathyroid fine-needle aspiration biopsy is not recommended except in unusual, difficult cases of pHPT and should not be performed if PCA is suspected (insufficient evidence).

Technetium Tc 99m sestamibi is the dominant radioisotope in parathyroid scintigraphy. Each sestamibi protocol (dual-phase, iodine 131 subtraction, single-photon emission computed tomog-

raphy) has individual strengths and weaknesses (eAppendix in the Supplement). Sensitivity in MGD is poor. Combined ultrasonography and sestamibi imaging increases localization accuracy and improves sensitivity (eAppendix in the Supplement). Although traditional computed tomography has little utility, the 4-dimensional computed tomography protocol has emerged as a useful modality, although sensitivity in MGD is limited.

- **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).
- **Recommendation 4-6:** Magnetic resonance imaging and venous sampling can be considered in cases of subsequent operation, difficult localization, or ionizing radiation contraindication (weak recommendation; low-quality evidence).

Preoperative Management

A daily intake of 1000 to 1200 mg of calcium is recommended for adults and appears appropriate for patients with pHPT as well. Dietary restriction of calcium is not advised in pHPT. Preoperative vitamin D repletion is advised and should be performed carefully in patients with hypercalciuria (eAppendix in the Supplement).

- **Recommendation 5-1:** Most patients with pHPT should follow Institute of Medicine guidelines for calcium intake (strong recommendation; moderate-quality evidence).
- **Recommendation 5-2:** Before parathyroidectomy, patients with pHPT who are vitamin D deficient can safely begin vitamin D supplementation (weak recommendation; low-quality evidence).

Subjective assessment of voice quality is an essential component of preoperative examination. Additional objective evaluation is recommended for subjective changes, surgeon-identified abnormalities, or any history of prior operations in which the vagus nerve or recurrent laryngeal nerve (RLN) was at risk (eAppendix in the Supplement).

- **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).

Hypercalcemic crisis is defined by a rapid-onset, albumin-corrected serum calcium level greater than 14 mg/dL and signs or symptoms of multiorgan dysfunction.[29] Intravenous fluid resuscitation and pharmacologic management are used to stabilize patients before expeditious parathyroidectomy. The presence of PCA should be considered (eAppendix in the Supplement).

- **Recommendation 5-4:** Patients with pHPT who present with hypercalcemic crisis should be medically managed, followed by parathyroidectomy (strong recommendation; low-quality evidence).

Intraoperative PTH Monitoring

Intraoperative PTH monitoring (IPM) provides real-time assessment of parathyroid function and has a major effect on focused operations when the surgeon removes an image-identified abnormal gland without additional dissection. The success of focused operations guided by IPM has been excellent, with cure rates as high as 97% to 99% (eTable 3 in the Supplement).[30] Focused operations guided solely by imaging studies without IPM can miss MGD, with failure rates that may be higher than accepted standards (eAppendix in the Supplement). For initial image-guided surgery, positive imaging directs where to start exploration, and the results of intraoperative PTH monitoring help to terminate it.

- **Recommendation 6-1:** When image-guided focused parathyroidectomy is planned, IPM is suggested to avoid higher operative failure rates (strong recommendation; moderate-quality evidence).

The accuracy of IPM depends on the protocol used. Surgeons should use a protocol that is practical, accurate, and reproducible and be aware of potential sources of error (eAppendix in the Supplement). In addition, IPM is useful in differential jugular venous sampling and ex vivo parathyroid aspiration (eAppendix in the Supplement).

- **Recommendation 6-2:** Surgeons who use IPM should use 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).

Minimally Invasive Parathyroidectomy

Approximately 85% of patients with pHPT have a solitary adenoma, the resection of which results in durable cure. Thus, surgeons have adapted a variety of methods to streamline parathyroidectomy and reduce the risk of complications, collectively termed *minimally invasive parathyroidectomy* (MIP). All MIP techniques are designed to limit dissection, hasten recovery, reduce postoperative discomfort, and reduce incision length. These techniques typically require preoperative imaging and other adjuncts.

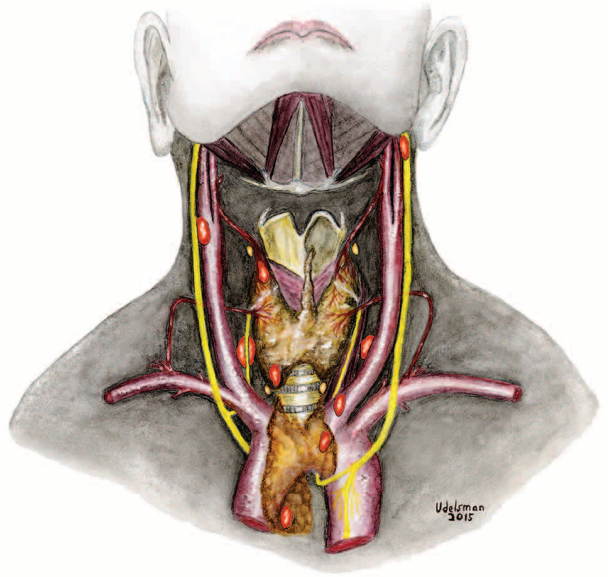
Regardless of MIP technique, specific strategies are advised to improve the likelihood of success (eAppendix in the Supplement), including selection by imaging results. Minimally invasive parathyroidectomy can achieve cure in 97% to 99% of selected patients when adjunctive IPM is used to confirm adequacy of resection (eAppendix in the Supplement).[31] During MIP, if IPM suggests residual hypersecreting tissue, conversion to bilateral exploration (BE) is warranted and has equivalent cure rates to planned BE.

- **Recommendation 7-1:** Defined as a focused dissection, MIP is ideally used in patients who appear clinically and by imaging to have a single parathyroid adenoma. It is not routinely recommended in patients with known or suspected high risk of MGD (strong recommendation; high-quality evidence).
- **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).
- **Recommendation 7-3:** During MIP, the discovery of MGD, the inability to identify an abnormal gland, or the failure to achieve an appropriate IPM decrease should prompt conversion to BE (strong recommendation; high-quality evidence).

Bilateral Exploration

In BE, all parathyroid glands should be identified and compared to deduce the presence of a single adenoma or MGD. Bilateral exploration has long-term success rates greater than 95% and low complication rates.[22,32] Familiarity with parathyroid anatomy, the loca-

Figure 1. Anatomical Relationships of Eutopic and Ectopic Parathyroid Glands



tions of eutopic (normal position) and ectopic glands (**Figure 1**), and the appearance of normal and abnormal glands (eAppendix in the Supplement) is essential.

- **Recommendation 8-1:** Bilateral exploration provides a time-tested standard of efficacy and safety in the definitive treatment of pHPT (strong recommendation; high-quality evidence).
- **Recommendation 8-2:** Planned BE is the preferred operative strategy in situations of discordant or nonlocalizing 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).
- **Recommendation 8-3:** Bilateral exploration 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).
- **Recommendation 8-4:** In lithium-induced pHPT, the surgical approach may be BE or MIP guided by imaging and IPM (weak recommendation; low-quality evidence).

Familial pHPT

In patients with a genetic predisposition for pHPT (eAppendix in the Supplement), the high likelihood of MGD and recurrent hypercalcemia necessitate a distinctive surgical approach with the goals of achieving eucalcemia for as long as possible, avoiding hypoparathyroidism, and facilitating potential subsequent operation for recurrence. Lifelong follow-up is critical.

- **Recommendation 9-1:** In patients with multiple endocrine neoplasia type 1–associated pHPT, subtotal parathyroidectomy is recommended as the index operation (strong recommendation; moderate-quality evidence).
- **Recommendation 9-2:** In multiple endocrine neoplasia type 2A–associated pHPT, resection of only visibly enlarged glands is recommended (weak recommendation; low-quality evidence).

Surgical Adjuncts

The most widely used surgical adjunct is IPM. Other adjuncts (eAppendix in the Supplement) can assist with confirmation of resected parathyroid tissue (frozen section analysis, ex vivo parathyroid aspiration), gland visualization (methylene blue, near infrared fluorescence or infrared spectroscopy), and gland localization (intraoperative ultrasonography, bilateral jugular venous sampling, or γ-probe guidance). Monitoring of the RLN is used less often in parathyroid than thyroid surgery but may play a role in subsequent operation. Adjuncts cannot replace judgment and experience.

Concurrent Thyroidectomy

In patients with pHPT, concomitant thyroid disease is frequent (12%-67%) (eAppendix in the Supplement). Concurrent thyroidectomy may be performed for thyroid disease that requires resection, suspicion of PCA, removal of an abnormal intrathyroidal parathyroid gland, or improved access.

- **Recommendation 11-1:** Patients undergoing parathyroidectomy should have preoperative thyroid evaluation because of the high rate of concomitant disease, which may require thyroid resection (strong recommendation; moderate-quality evidence).

Compared with intraoperative thyroid examination, preoperative ultrasonography is more sensitive and specific for clinically significant thyroid disease and is associated with a 5-fold lower rate of thyroid resection.[33] Preoperative identification of thyroid disease may facilitate performance of the most appropriate index operation, reduce complications, and avoid future reoperation (eAppendix in the Supplement).

- **Recommendation 11-2:** In patients with concomitant pHPT and thyroid disease that requires resection, thyroid resection should be performed at the time of parathyroidectomy (strong recommendation; moderate-quality evidence).
- **Recommendation 11-3:** Evaluation for concomitant thyroid disease in patients undergoing parathyroidectomy for pHPT should follow evidence-based guidelines (strong recommendation; high-quality evidence).
- **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).

Parathyroid Carcinoma

Parathyroid cancer accounts for approximately 1% of all cases of pHPT and typically presents with very high PTH and calcium levels (eTable 4 in Supplement).[34] Parathyroidectomy is the only curative treatment for PCA.

- **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).

- **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 evidence).
- **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).
- **Recommendation 12-5:** Adjuvant external beam radiotherapy should not be routinely performed after surgical resection of PCA and is reserved as a palliative option (strong recommendation; low-quality evidence).
- **Recommendation 12-6:** Patients with functional PCA should undergo regular surveillance by testing serum calcium and PTH levels (strong recommendation; low-quality evidence).

Autotransplantation and Cryopreservation

Autotransplantation is the most reliable method to preserve function when a gland cannot be kept viable on its vascular pedicle. The arterial perfusion of parathyroid glands that have been manipulated but are left in situ should be assessed. 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 were the last (eAppendix in the Supplement).

- **Recommendation 13-1:** Immediate autotransplantation is recommended for normal parathyroid glands that appear devascularized (strong recommendation; low-quality evidence).

Immediate Postoperative Care

Although a common finding, especially in vitamin D–deficient patients or those with malabsorption for any reason (eg, celiac disease or prior bariatric surgery), symptomatic hypocalcemia is typically transient and managed as an outpatient.[32,35,36] Patients undergoing BE have significantly higher rates of mild and severe hypocalcemic symptoms.[37,38] The reported rates of moderate postoperative hypocalcemia range from 5% to 47%.[39] After initial parathyroid surgery, permanent hypoparathyroidism is rare (0%-3.6%).[32,35-37]

- **Recommendation 14-1:** The operative note should detail the findings and events of parathyroidectomy (insufficient evidence).
- **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 emergency decompression (strong recommendation; low-quality evidence).
- **Recommendation 14-3:** Short-term calcium and/or vitamin D supplementation for prophylaxis against hypocalcemia should be considered after parathyroidectomy (weak recommendation; low-quality evidence).

Outpatient parathyroidectomy can be performed in selected patients. An overnight stay may be appropriate for patients undergoing subsequent operation, extensive exploration, or subtotal parathyroidectomy or those with profound vitamin D deficiency, social issues, or expected nonadherence.

- **Recommendation 14-4:** Outpatient parathyroid surgery can be considered in selected patients (weak recommendation; low-quality evidence).

The assessment of cure and complications (prolonged hypoparathyroidism, permanent RLN paralysis) requires evaluation for at least 6 months. Longitudinal testing should include calcium, PTH, and 25-hydroxyvitamin D levels. Achieving normal vitamin D levels postoperatively will help absorption of calcium and normalization of PTH levels and may improve BMD (eAppendix in the Supplement).

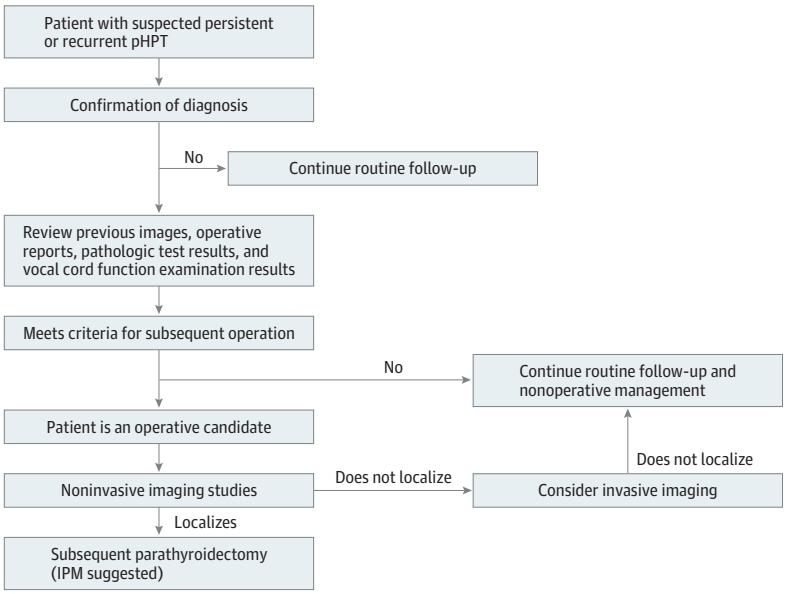
- **Recommendation 14-5:** After apparently successful parathyroidectomy, calcium intake should follow the Institute of Medicine Dietary Reference Intakes (strong recommendation; moderate-quality evidence).
- **Recommendation 14-6:** Patients who are vitamin D deficient should receive vitamin D supplementation after apparently successful parathyroidectomy (strong recommendation; moderate-quality evidence).
- **Recommendation 14-7:** At 6 months, surgeons individually or in conjunction with the multidisciplinary care team should assess postparathyroidectomy patients for cure and evidence of long-term complications (strong recommendation; low-quality evidence).

Cure and Failure

The goal of parathyroidectomy is cure. Cure rates for parathyroidectomy in sporadic pHPT should approach 95% to 99%. Although there is no role for routine PTH measurement in the normocalcemic patient in the immediate postoperative period, failure to normalize PTH levels at 6 months or longer can signify early operative failure. In normocalcemic pHPT, the PTH level must also normalize to indicate cure. In patients with inherited forms of pHPT, a different end point of care pertains (eAppendix in the Supplement).

- **Recommendation 15-1a:** Cure after parathyroidectomy is defined as the reestablishment of normal calcium homeostasis lasting a minimum of 6 months (strong recommendation; high-quality evidence).
- **Recommendation 15-1b:** Patients with normocalcemic pHPT who have persistently elevated PTH levels 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).
- **Recommendation 15-2:** Surgeons should choose an operative approach that in their hands carries a high cure rate, low-risk profile, and cost comparable to other available techniques (strong recommendation; low-quality evidence).
- **Recommendation 15-3:** In normocalcemic pHPT, the definition of cure must include normal calcium and PTH levels more than 6 months after surgery (insufficient evidence).

Figure 2. Algorithm for the Evaluation and Management of Persistent or Recurrent Primary Hyperparathyroidism (pHPT)



IPM indicates intraoperative parathyroid hormone monitoring.

Operative failure remains the most common complication of parathyroidectomy. Failure may be predicted by an incomplete decrease in IPM levels or kinetic analysis. Diagnosis of failure requires discontinuation of calcium use and a stepwise evaluation (eAppendix in the Supplement). Surgeons should be cognizant of their failure rates.

- **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 more than 6 months after parathyroidectomy (strong recommendation; high-quality evidence).

Management of Other Complications

Laryngeal reinnervation does not restore normal vocal fold movement, but it may improve voice strength, reduce the risk of aspiration, and decrease the need for postoperative vocal cord medialization and injections.

- **Recommendation 16-1:** When RLN transection is recognized during parathyroidectomy, a reinnervation procedure should be attempted (strong recommendation; low-quality evidence).

The symptoms of postoperative hypoparathyroidism include perioral numbness and fingertip paresthesias, which can also occur in euparathyroid bone hunger or transient hypoparathyroidism (eAppendix in the Supplement). Severe postoperative hypocalcemia is rare. Patients may require temporary postoperative calcium administration and calcitriol to avoid such symptoms (eAppendix in the Supplement). In contrast, prolonged hypoparathyroidism is a chronic condition of such diminished parathyroid function that ongoing calcium and calcitriol treatment is required for 6 to 12 months.[40]

- **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).

Subsequent Operation

Reoperative parathyroidectomy is defined as any prior cervical operation that placed the RLN at risk. In persistent or recurrent pHPT, subsequent operation is often recommended to achieve biochemical cure. Because cure rates are lower (82%-98%) (eAppendix in the Supplement) and risks are higher, many surgeons use stricter indications for subsequent operation than for initial surgery.[41,42] A careful data evaluation, assessment for surgical indications beyond the biochemical diagnosis, and positive imaging results are essential; this algorithm is detailed in **Figure 2**. Intraoperative PTH monitoring and other adjuncts are often used.

- **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 before the decision to proceed with surgery or nonoperative management (strong recommendation; low-quality evidence).
- **Recommendation 17-3:** Intraoperative PTH monitoring 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 and efficiently as possible.

ARTICLE INFORMATION

Accepted for Publication: May 19, 2016.

Published Online: August 10, 2016. doi:10.1001/jamasurg.2016.2310

Author Affiliations: Department of Surgery, University Hospitals/Case Medical Center, Cleveland, Ohio (Wilhelm); Department of Surgery, Medical College of Wisconsin, Milwaukee (Wang); Department of Surgery, Brigham and Women's Hospital, Boston, Massachusetts (Ruan); Department of Surgery, Columbia University College of Physicians and Surgeons, New York, New York (Lee); Department of Pathology, University of Toronto, Toronto, Ontario, Canada (Asa); Department of Surgery, University of California San Francisco Medical Center, San Francisco (Duh); Department of Surgery, Boston University, Boston, Massachusetts (Doherty); Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico (Herrera); Department of Surgery, University of Calgary, Calgary, Alberta, Canada (Pasieka); Department of Surgery, MD Anderson Cancer Center, Houston, Texas (Perrier); Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York (Silverberg); Department of Surgery, Vanderbilt University Medical Center, Nashville, Tennessee (Solórzano); Department of Surgery, Northwestern University, Chicago, Illinois (Sturgeon); Department of Radiology, University of Pittsburgh, Pittsburgh, Pennsylvania (Tublin); Department of Surgery, Yale University, New Haven, Connecticut (Udelsman); Department of Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania (Carty).

Conflict of Interest Disclosures: None reported.

Additional Information: Dr Carty is the chair of the AAES Parathyroidectomy Guidelines Writing Group.

REFERENCES

1. Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab*. 2014;99(10):3561-3569.

2. Marcocci C, Bollerslev J, Khan AA, Shoback DM. Medical management of primary hyperparathyroidism: proceedings of the fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. *J Clin Endocrinol Metab*. 2014;99(10):3607-3618.

3. Eastell R, Brandi ML, Costa AG, D'Amour P, Shoback DM, Thakker RV. Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab*. 2014;99(10):3570-3579.

4. Silverberg SJ, Clarke BL, Peacock M, et al. Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab*. 2014;99(10):3580-3594.

5. Qaseem A, Snow V, Owens DK, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. The development of clinical practice guidelines and guidance statements of the American College of Physicians: summary of methods. *Ann Intern Med*. 2010;153(3):194-199.

6. Bilezikian JP, Silverberg SJ. Normocalcemic primary hyperparathyroidism. *Arq Bras Endocrinol Metabol*. 2010;54(2):106-109.

7. Evans DB, Rich TA, Cote GJ. Surgical management of familial hyperparathyroidism. *Ann Surg Oncol*. 2007;14(5):1525-1527.

8. Stålberg P, Carling T. Familial parathyroid tumors: diagnosis and management. *World J Surg*. 2009;33(11):2234-2243.

9. Thakker RV, Newey PJ, Walls GV, et al; Endocrine Society. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab*. 2012;97(9):2990-3011.

10. Awad SS, Miskulin J, Thompson N. Parathyroid adenomas versus four-gland hyperplasia as the cause of primary hyperparathyroidism in patients with prolonged lithium therapy. *World J Surg*. 2003;27(4):486-488.

11. Pasieka JL, Parsons L, Jones J. The long-term benefit of parathyroidectomy in primary hyperparathyroidism: a 10-year prospective surgical outcome study. *Surgery*. 2009;146(6):1006-1013.

12. Pasieka JL, Parsons LL. Prospective surgical outcome study of relief of symptoms following surgery in patients with primary hyperparathyroidism. *World J Surg*. 1998;22(6):513-518.

13. Sheldon DG, Lee FT, Neil NJ, Ryan JA Jr. Surgical treatment of hyperparathyroidism improves health-related quality of life. *Arch Surg*. 2002;137(9):1022-1026.

14. Ambrogini E, Cetani F, Cianferotti L, et al. Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective, randomized clinical trial. *J Clin Endocrinol Metab*. 2007;92(8):3114-3121.

15. Zanocco K, Angelos P, Sturgeon C. Cost-effectiveness analysis of parathyroidectomy for asymptomatic primary hyperparathyroidism. *Surgery*. 2006;140(6):874-881.

16. Vestergaard P, Mosekilde L. Cohort study on effects of parathyroid surgery on multiple outcomes in primary hyperparathyroidism. *BMJ*. 2003;327(7414):530-534.

17. Rolighed L, Amstrup AK, Jakobsen NF, et al. Muscle function is impaired in patients with "asymptomatic" primary hyperparathyroidism. *World J Surg*. 2014;38(3):549-557.

18. Reiher AE, Mazeh H, Schaefer S, Gould J, Chen H, Sippel RS. Symptoms of gastroesophageal reflux disease improve after parathyroidectomy. *Surgery*. 2012;152(6):1232-1237.

19. Mollerup CL, Vestergaard P, Frøkjaer VG, Mosekilde L, Christiansen P, Blichert-Toft M. Risk of renal stone events in primary hyperparathyroidism before and after parathyroid surgery: controlled retrospective follow up study. *BMJ*. 2002;325(7368):807.

20. Silverberg SJ, Brown I, Bilezikian JP. Age as a criterion for surgery in primary hyperparathyroidism. *Am J Med*. 2002;113(8):681-684.

21. Rao DS, Phillips ER, Divine GW, Talpos GB. Randomized controlled clinical trial of surgery versus no surgery in patients with mild asymptomatic primary hyperparathyroidism. *J Clin Endocrinol Metab*. 2004;89(11):5415-5422.

22. Abdulla AG, Ituarte PH, Harari A, Wu JX, Yeh MW. Trends in the frequency and quality of parathyroid surgery: analysis of 17,082 cases over 10 years. *Ann Surg*. 2015;261(4):746-750.

23. Zanocco K, Sturgeon C. How should age at diagnosis impact treatment strategy in asymptomatic primary hyperparathyroidism? a cost-effectiveness analysis. *Surgery*. 2008;144(2):290-298.

24. Rubin MR, Bilezikian JP, McMahon DJ, et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. *J Clin Endocrinol Metab*. 2008;93(9):3462-3470.

25. Rodgers SE, Hunter GJ, Hamberg LM, et al. Improved preoperative planning for directed parathyroidectomy with 4-dimensional computed tomography. *Surgery*. 2006;140(6):932-940.

26. Solorzano CC, Carneiro-Pla D. Minimizing cost and maximizing success in the preoperative localization strategy for primary hyperparathyroidism. *Surg Clin North Am*. 2014;94(3):587-605.

27. Lubitz CC, Hunter GJ, Hamberg LM, et al. Accuracy of 4-dimensional computed tomography in poorly localized patients with primary hyperparathyroidism. *Surgery*. 2010;148(6):1129-1137.

28. Wang TS, Cheung K, Farrokhyar F, Roman SA, Sosa JA. Would scan, but which scan? a cost-utility analysis to optimize preoperative imaging for primary hyperparathyroidism. *Surgery*. 2011;150(6):1286-1294.

29. Starker LF, Björklund P, Theoharis C, Long WD III, Carling T, Udelsman R. Clinical and histopathological characteristics of hyperparathyroidism-induced hypercalcemic crisis. *World J Surg*. 2011;35(2):331-335.

30. Irvin GL III, Carneiro DM, Solorzano CC. Progress in the operative management of sporadic

primary hyperparathyroidism over 34 years. *Ann Surg*. 2004;239(5):704-708.

31. McCoy KL, Chen NH, Armstrong MJ, et al. The small abnormal parathyroid gland is increasingly common and heralds operative complexity. *World J Surg*. 2014;38(6):1274-1281.

32. Allendorf J, DiGorgi M, Spanknebel K, Inabnet W, Chabot J, Logerfo P. 1112 consecutive bilateral neck explorations for primary hyperparathyroidism. *World J Surg*. 2007;31(11):2075-2080.

33. Milas M, Mensah A, Alghoul M, et al. The impact of office neck ultrasonography on reducing unnecessary thyroid surgery in patients undergoing parathyroidectomy. *Thyroid*. 2005;15(9):1055-1059.

34. van Heerden JA, Weiland LH, ReMine WH, Walls JT, Purnell DC. Cancer of the parathyroid glands. *Arch Surg*. 1979;114(4):475-480.

35. Udelsman R, Åkerström G, Biagini C, et al. The surgical management of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab*. 2014;99(10):3595-3606.

36. Stewart ZA, Blackford A, Somervell H, et al. 25-hydroxyvitamin D deficiency is a risk factor for symptoms of postoperative hypocalcemia and secondary hyperparathyroidism after minimally invasive parathyroidectomy. *Surgery*. 2005;138(6):1018-1025.

37. Bergenfelz A, Lindblom P, Tibblin S, Westerdahl J. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: a prospective randomized controlled trial. *Ann Surg*. 2002;236(5):543-551.

38. Roman SA, Sosa JA, Pietrzak RH, et al. The effects of serum calcium and parathyroid hormone changes on psychological and cognitive function in patients undergoing parathyroidectomy for primary hyperparathyroidism. *Ann Surg*. 2011;253(1):131-137.

39. Mittendorf EA, Merlino JI, McHenry CR. Post-parathyroidectomy hypocalcemia: incidence, risk factors, and management. *Am Surg*. 2004;70(2):114-119.

40. Stack BC Jr, Bimston DN, Bodenner DL, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Disease state clinical review: postoperative hypoparathyroidism—definitions and management. *Endocr Pract*. 2015;21(6):674-685.

41. Karakas E, Müller HH, Schlosshauer T, Rothmund M, Bartsch DK. Reoperations for primary hyperparathyroidism: improvement of outcome over two decades. *Langenbecks Arch Surg*. 2013;398(1):99-106.

42. Weber CJ, Sewell CW, McGarity WC. Persistent and recurrent sporadic primary hyperparathyroidism: histopathology, complications, and results of reoperation. *Surgery*. 1994;116(6):991-998.