The Surgical Management of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Fourth International Workshop

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Objective: The surgical management of primary hyperparathyroidism (PHPT) has undergone considerable advances over the past two decades. The purpose of this report is to review these advances.

Participants: This subgroup was constituted by the Steering Committee of the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism to address key questions related to the surgical management of PHPT.

Evidence: Data since the last International Workshop were presented and discussed in detail. The topics included improvements in preoperative imaging, intraoperative adjuncts, refinements in local and regional anesthesia, and rapid intraoperative PTH assays.

Consensus Process: Questions were developed by the International Task Force on PHPT. A comprehensive literature search for relevant studies was undertaken. After extensive review and discussion, the subgroup agreed on what recommendations should be made to the Expert Panel regarding surgical approaches to parathyroidectomy.

Conclusions: 1) All patients with PHPT who meet surgical criteria should be referred to an experienced endocrine surgeon to discuss the risks, benefits, and potential complications of surgery. 2) Patients who do not meet surgical criteria and in whom there are no medical contraindications to surgery may request a visit with an experienced endocrine surgeon. Alternatively, a multidisciplinary endocrine conference with surgeon involvement could be employed to address all relevant issues. 3) Imaging is not a diagnostic procedure; it is a localization procedure to help the surgeon optimize the operative plan. 4) The frequency of hereditary forms of PHPT may be underappreciated and needs to be assessed with increased vigilance. And 5) surgery is likely to benefit patients due to high cure rates, low complication rates, and the likelihood of reversing skeletal manifestations. **(*J Clin Endocrinol Metab* 99: 0000–0000, 2014)**

The surgical management of patients with primary hyperparathyroidism (PHPT) has undergone considerable advances over the past two decades. Improvements in preoperative imaging and intraoperative adjuncts, including rapid PTH assays, have resulted in increased adoption of minimally invasive surgical techniques. Yet, there remain several areas of controversy, including the indications for surgery, the extent of preoperative evaluation,

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Abbreviations: CaSR, calcium-sensing receptor; CT, computed tomography; FHH, familial hypocalciuric hypercalcemia; FIHPT, familial isolated hyperparathyroidism; HPT-JT, hyperparathyroidism-jaw tumor; MEN, multiple endocrine neoplasia; MIP, minimally invasive parathyroidectomy; PHPT, primary hyperparathyroidism.

the role of imaging studies, operative options including the role of minimally invasive techniques, the role of intraoperative adjuncts, and the diagnosis and management of patients with hereditary forms of PHPT.

Materials and Methods

In connection with the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism, participants representing an international constituency with interest and expertise in asymptomatic PHPT constituted four Workshop Panels that developed 12 key questions.

1) What are the indications for surgery?
2) What is the appropriate preoperative evaluation?
3) What is the appropriate biochemical confirmation?
4) What are the appropriate imaging studies?
5) What are the operative options?
   5.1 Are there additional operative approaches?
6) How and when should intraoperative PTH analysis be employed?
7) What is the role of neuromonitoring?
8) What is the role of an intraoperative gamma probe?
9) Are there special considerations for surgery for hereditary syndromes?
10) What are the complications of parathyroid surgery?
11) What are the conclusions?
12) What are the future directions?

They then convened in an open 3-day conference, September 19–21, 2013, in Florence, Italy, when a series of presentations and discussions addressed these questions. A Surgical Taskforce, selected by the organizing committee, was represented by surgeons and imaging experts from the United States, Sweden, Italy, and Austria. A smaller subcommittee, the Expert Panel, then met in a closed session to reach evidence-based consensus.

1) What are the indications for surgery?

It is important to emphasize that surgery is the only potentially curable option for patients with PHPT. There is universal agreement that all symptomatic patients, as well as those with significant signs of disease (renal or bone manifestations), have clear indications for surgical treatment. In addition, young patients (<50 y of age) and those who have other biochemical indicators as reviewed in earlier manuscripts should undergo surgical exploration (1, 2). Less certain are patients who do not meet these strict criteria but have neurocognitive symptoms that are elicited or self-reported. Some prospective trials have demonstrated that surgical correction of PHPT results in symptomatic improvement in a subset of these patients, although it is not possible to predict which of these patients will experience symptomatic improvement (3, 4). This area is covered in an accompanying report by Silverberg et al (5).

2) What is the appropriate preoperative evaluation?

A carefully performed history and physical examination is the basis for all patient evaluations. The history must include an assessment of head and neck radiation exposure, previous operative procedures, and a careful review of all medications, including lithium, thiazide diuretics, calcium-containing products, vitamin D, anticonvulsants, and anticoagulants. The surgeon must elucidate coexistent medical conditions, particularly those that can influence surgical or anesthetic management. The history should evaluate subtle neurocognitive symptoms that are commonly reported in PHPT. The family history is designed to determine the likelihood of a genetic form of PHPT such as the multiple endocrine neoplasia (MEN) syndromes, the hyperparathyroidism-jaw tumor (HPT-JT) syndrome, and heterozygous calcium-sensing receptor (*CaSR*) gene mutations, causing familial hypocalciuric hypercalcemia (FHH). Eliciting a history of hypercalcemia in childhood or young adulthood can be a clue to the presence of FHH. Identification of family members with endocrine tumors of the pancreas or pituitary as well as those with recurrent peptic ulcer disease may suggest MEN 1 syndrome. Recent data suggest that as many as 10% of younger patients (<45 y of age) with apparent sporadic PHPT harbor a germline mutation in one of the genes associated with familial forms of PHPT (6). Even elderly patients with PHPT have a 3–5% risk of harboring a mutation of genes encoding for cyclin-dependent kinase inhibitors that are responsible for a higher risk of development of PHPT in first-degree relatives (7). A family history of nephrolithiasis or premature osteoporosis may be the first indication of a genetic basis for the PHPT. Genetic screening is indicated in high-risk patients.

The physical examination includes both an overall assessment of cardiovascular and pulmonary reserve and a focused endocrine evaluation. The presence of a goiter or evidence of previous cervical or mediastinal surgery is a critical component. Thyroid conditions including nodular thyroid disease must be assessed and potentially reconciled. Thyroid nodules may require biopsy, and a patient with severe hypercalcemia and a palpable neck mass is at risk for parathyroid carcinoma but is more likely to have a parathyroid adenoma and coincident thyroid nodule. Evaluation of vocal cord function should be considered in patients referred for surgery. It is mandatory in patients

who have had previous cervical or mediastinal surgery and in patients with symptoms or signs of vocal cord dysfunction. It is easily performed by indirect mirror examination or flexible fiber optic laryngoscopy.

3)What is the appropriate biochemical confirmation?

The basis for the diagnosis of PHPT is the presence of an elevated serum calcium level and an inappropriate elevation of serum PTH in the setting of normal renal function. The biochemical diagnosis and recommendations for the evaluation of patients with asymptomatic PHPT has been extensively reviewed by Bilezikian et al (8) in an accompanying manuscript. Vitamin D repletion is suggested for operative candidates who are vitamin D deficient.

4) What are the appropriate imaging studies?

Imaging is a localization procedure used to guide the surgeon planning the surgical strategy. It is not a diagnostic procedure. Accordingly, there is no reason to obtain an imaging study if surgery is not planned. Furthermore, negative or discordant imaging studies should not inhibit referral to an experienced parathyroid surgeon (9). It is the surgeon in concert with the radiologist and nuclear medicine physician who should organize the imaging studies because it is the surgeon who must evaluate their qualities and sensitivities in the local environment to plan for operative intervention. Multiple imaging studies are available and differentiated into noninvasive and invasive. This manuscript is focused on the asymptomatic patient in whom invasive studies are rarely indicated.

Noninvasive imaging studies include cervical ultrasound, nuclear scintigraphy, computed tomography (CT), magnetic resonance imaging, and positron emission tomography scans (10). Ultrasound and nuclear medicine studies as well as CT scans are the most commonly employed (11). Parathyroid ultrasound requires skilled imagers and interpreters with knowledge of parathyroid embryology and anatomy to access parathyroid glands in eutopic and ectopic positions (12). In addition, ultrasound is an exquisitely sensitive technique to evaluate the thyroid gland for synchronous nodules. However, concomitant thyroid disease reduces the true positive results of both ultrasound and sestamibi scans (13). The ultrasonographer physician will focus on the location, size, morphology, echo-texture, and vascular characteristics of putative parathyroid glands. Ultrasound is limited in its ability to evaluate retroesophageal lesions and cannot penetrate bony structures such as the clavicles or sternum. Accordingly, evaluation of mediastinal parathyroid glands is quite limited. Ultrasound is also attractive because of its low expense and absence of ionizing radiation exposure, and it can be performed by the operative surgeon (14).

A variety of nuclear scintigraphic agents and techniques have been employed (15, 16). The preferred agent utilizes ^{99m}Tc-sestamibi scans imaged with single photon emission CT (17–19). Sestamibi scans are relatively inexpensive, and the radiation dose is acceptable. Furthermore, sestamibi scans can be very helpful in identifying ectopic parathyroid glands, including those in retroesophageal and mediastinal locations. Recent improvements in CT scans have increased their sensitivity by employing four-dimensional techniques (20). The fourth dimension refers to time as multiple scans are obtained after administration of iv contrast agents. The exquisite anatomic detail seen on high-quality four-dimensional CT scans can be very beneficial. However, CT scans expose the thyroid gland to ionizing radiation, and this must be considered particularly in young patients where the theoretical risk of thyroid cancer is highest (21).

Imaging studies will occasionally suggest enlargement of more than one parathyroid gland. In this setting, multigland disease must be considered. Furthermore, it is unusual for any imaging study to demonstrate that all four parathyroid glands are enlarged in patients with multigland disease (22). The more common finding is asymmetric multigland enlargement where some of the glands appear normal on imaging.

5) What are the operative options?

There are a wide variety of operative options for patients with PHPT (23). The traditional approach employs general endotracheal anesthesia and bilateral cervical exploration regardless of the preoperative imaging studies. This is preferred in some surgical centers because preoperative imaging has inadequate sensitivity to reliably demonstrate multigland parathyroid disease. Bilateral surgical exploration as described below under bilateral cervical exploration is an excellent operation when it is performed by experienced surgeons and is associated with low complication rates and curative rates in the range of 95–98%. Bilateral cervical exploration is also the ideal operation for most patients with multigland disease, including those with genetic disease.

Minimally invasive approaches

Minimally invasive approaches have gained progressive acceptance as an alternative safe and effective technique over the past two decades (24–26). Although the term "minimally invasive parathyroidectomy" (MIP) is imprecise and subject to multiple interpretations, it implies an image-guided, focused operation designed to minimize tissue trauma. The etiology for PHPT for the ma-

jority (85%) of patients is a single adenoma that, when removed, results in a durable cure (24). Accordingly, surgeons have utilized preoperative imaging to suggest the location of a presumptive causative parathyroid gland and remove it, often under local or regional anesthesia, employing small incisions and in some centers same-day discharge.

These minimally invasive approaches employ an open technique or a variety of endoscopic approaches. They share the concept that the surgeon will identify and remove the image-identified enlarged parathyroid gland and generally employ an intraoperative adjunct to determine whether additional hyperfunctioning PTH-secreting glands remain in situ. Rapid intraoperative PTH assays (see How and when should intraoperative PTH analysis be employed?) have proven remarkably accurate in either confirming the adequacy of resection or predicting residual disease (25, 27). In the latter situation, the surgeon is prompted to continue the exploration and resect additional abnormal parathyroid glands.

These minimally invasive techniques have been adopted at many centers where parathyroid surgery is routinely performed. The data from these centers demonstrate curative results that exceed 98% and nerve injury rates of 1% or less (24, 25). They are frequently performed on an outpatient basis, avoid general anesthesia, and reduce the costs associated with surgical intervention. These procedures are not recommended in centers that do not have sophisticated imaging, intraoperative PTH assays, and experienced endocrine surgeons.

Endoscopic approaches

Endoscopic techniques were conceived as minimally invasive operations (28, 29). The endoscope should be regarded as a tool to maintain or enhance operative visualization, despite an abbreviated incision (30). This does not necessarily coincide with a less invasive procedure. The three most common endoscopic techniques are: 1) total endoscopic parathyroidectomy using a 5-mm 30° endoscope (30); 2) parathyroidectomy by a lateral approach using a 0° endoscope (28); and 3) video-assisted parathyroidectomy by central neck access using a 5-mm 30° endoscope (29).

The first two techniques involve CO_2 insufflation that should be maintained at a pressure below 9 mm Hg to avoid pneumomediastinum with consequent hypercapnia. The lateral cervical approach offers an excellent view of superior adenomas but is less viable for inferior adenomas, which tend to be more anterior and difficult to reach with a 0° angle endoscope. Moreover, central access accommodates bilateral exploration, which may be necessary during endoscopic approaches that require preoperative localization of a single adenoma, although the option of bilateral exploration remains a keystone of the surgical treatment of PHPT. Endoscopic parathyroidectomy requires careful patient selection to achieve positive outcomes and acceptable conversion rates. Contraindications are previous extensive neck surgery or a suspicion of malignant disease. In addition, a large goiter can obstruct the view and limit dissection of a parathyroid adenoma and other critical structures. Also, large parathyroid adenomas (exceeding 3 cm) are not optimally approached endoscopically. Ideal candidates are patients who present with a single, well-localized adenoma in a virgin neck, and 70–78% of patients with sporadic PHPT are appropriate. This varies by country, mainly due to the incidence of endemic goiter (29).

Most endoscopic parathyroid surgeons prefer general anesthesia, which facilitates insufflation and/or robust external retraction. However, no contraindications limit locoregional anesthesia as long as an adequate unilateral or bilateral cervical block can be obtained (31, 32). Conversion to open surgery is necessary in less than 10% of cases because of severe thyroiditis, inability to locate or extract an ectopic parathyroid adenoma, or inaccessible mediastinal parathyroid adenomas (33).

Are there additional operative approaches?

Thorascopic and transcervical-mediastinal approaches have been used successfully to resect ectopic mediastinal parathyroid adenomas. However, most ectopic mediastinal parathyroid glands can be resected through a cervical approach. A variety of additional approaches have been recently developed in an attempt to avoid a cervical incision. These include endoscopic approaches through the axilla, breast, chest, retroauricular space, and floor of the mouth. Some employ robotic assistance. All require significant incremental dissection to create adequate working space, and none are minimally invasive. The costs, increased operative time, and potential risks are likely to outweigh the advantage of avoiding a small neck incision.

Bilateral cervical exploration

Bilateral cervical exploration under general anesthesia has been the standard for the definitive treatment of sporadic PHPT (23). The results are excellent, with cure rates in the 95–98% range, and the complication rate is very low when the operation is performed by an experienced endocrine surgeon. Bilateral exploration can be performed through an abbreviated cosmetically appealing incision as an outpatient procedure. Although minimally invasive techniques have become increasingly adopted, all parathyroid surgeons must be able to perform a standard bilateral cervical exploration because even the "ideal single-

adenoma patient" may have occult multigland disease. There remain subsets of patients who are suboptimal candidates for minimally invasive techniques. These include patients with familial hyperparathyroidism as well as those with sporadic or pharmacologically induced disease (lithium) who harbor multigland hyperplasia. These patients usually require examination of all of their parathyroid glands.

Advocates for routine bilateral cervical exploration have noted that although intraoperative PTH levels may fall sufficiently to satisfy the "Miami criterion," residual anatomically enlarged parathyroid glands may remain in situ (34). They suggest that these residual enlarged glands are likely to cause persistent or recurrent disease. Furthermore, multigland disease occurs in 10–15% of unselected patients with sporadic PHPT and is more frequent in patients with mild hypercalcemia, in some young patients with nephrolithiasis, and in postmenopausal females who may have coincident vitamin D deficiency and/or mild subclinical renal impairment. These patients also have an increased incidence of "double adenomas" with two enlarged and two normal-sized glands (35, 36). Patients with familial PHPT also have multigland disease and usually require a bilateral exploration. Furthermore, any patient with apparent sporadic PHPT could represent an index case of familial disease, and bilateral exploration might be required to demonstrate multiple, but often, asymmetric enlarged parathyroid glands.

Bilateral cervical exploration may also be indicated for patients with apparent sporadic disease who have nonconvincing preoperative localization studies where bilateral multigland disease is more likely. In addition, patients with a past or current history of lithium therapy are likely to benefit from bilateral exploration (37). Patients who require operative treatment of concurrent thyroid disease may also benefit from bilateral cervicotomy. It must also be recognized that the availability of rapid intraoperative PTH assays is a luxury not available to most surgeons throughout the world. There have emerged two schools of thought among parathyroid surgeons about the appropriate use of routine bilateral cervical vs focused approaches in patients with PHPT. Although there is no clear consensus, both techniques yield excellent cure and minimal complications rates when the operation is performed by an experienced surgeon.

6) How and when should intraoperative PTH analysis be employed?

Intraoperative PTH assays are being employed with ever-increasing frequency during parathyroid surgery. They are required during MIP when the surgeon excises an image-identified, enlarged parathyroid gland but does not necessarily identify additional normal parathyroid glands. In this setting, independent confirmation is required to prove that residual abnormally secreting parathyroid glands are not left in situ. Because PTH has a mean circulating half-life of 3.5 to 4 minutes in patients with normal renal function, it is the ideal substrate to measure to prove that a curative procedure has been performed. Conversely, if postresection PTH values do not fall appropriately, the surgeon will be prompted to perform additional exploration to identify and resect a second adenoma or multiple enlarged parathyroid glands. Controversy exists about what criteria of PTH decay should be employed to confirm operative cure (38–40). The most commonly employed algorithm utilizes the Miami criterion, requiring a PTH fall of 50% compared to the highest of either the premanipulation or pre-excision sample (38, 41).

This criterion has the potential of yielding misleading results if PTH stimulation results from surgical manipulation (42, 43). This issue can be obviated by using both premanipulation and pre-excision PTH baseline samples. In addition, patients with genetic disease are more likely to have inadequate surgery if more rigid incremental criteria, such as a fall into the normal range, are not employed (36, 44, 45). A mathematical modeling technique was recently developed and embedded in software to allow surgeons to perform PTH cure analysis with greater accuracy (46). Intraoperative PTH assays are useful adjuncts during parathyroid surgery. They are essential, if focused approaches are employed, and obviate the need to identify normal parathyroid glands (47). They will not, however, replace the single most important criterion for excellent outcomes—an experienced parathyroid surgeon (35). The rapid PTH assay can also analyze an aspirate of a resected parathyroid gland to prove that the tissue is of parathyroid origin, thereby replacing frozen section analyses.

7) What is the role of neuromonitoring?

Neuromonitoring of vocal cord function during parathyroid surgery has been advocated by some surgeons; however, it requires an endotracheal tube and general anesthesia. Furthermore, in awake, nonintubated patients, intraoperative vocal cord assessment is easily obtained by listening to the patient's voice. Neuromonitoring is not recommended as a routine adjunct for parathyroid surgery.

8) What is the role of an intraoperative gamma probe?

Utilization of an intraoperative gamma probe to aid the surgeon to identify hyperfunctioning parathyroid glands as assessed by sestamibi uptake has been advocated by some parathyroid surgeons. The vast majority of parathy-

roid surgeons, including this panel, do not advocate this technique, especially for initial exploration.

9) Are there special considerations for surgery for hereditary syndromes?

Parathyroidectomy in the setting of hereditary PHPT is more challenging, and these patients are at higher risk of persistent and recurrent disease. Accordingly, special considerations are employed for this population of patients. The extent of parathyroid resection determines whether normocalcemia is achieved and for how long, the risk of hypoparathyroidism, the risk of surgical complications such as recurrent laryngeal nerve injury, and the risks and ease of parathyroid reoperations (48).

Hereditary forms of PHPT account for 5–10% of cases (6, 49). They are associated with MEN 1 (due to *MEN1* gene mutations), MEN 2A (*RET* oncogene mutations; (MEN 2B, also named MEN 3, is rarely associated with PHPT), rare MEN 4 syndromes (*CDKN1B* mutations), and the HPT-JT syndrome. Familial isolated hyperparathyroidism (FIHPT) includes patients with *MEN1* gene mutations, where other endocrinopathies are not expressed, and rare HPT-JT, due to a mutation of the *HRPT2/CDC73*, parafibromin gene. It also includes FHH, caused by a heterozygous mutation in the *CaSR* gene, and infants with homozygous *CaSR* gene mutations, causing neonatal severe PHPT with marked four-gland hyperplasia and the need for urgent parathyroidectomy (50–53).

All parathyroid cells in a patient with hereditary PHPT are mutated. Depending on the disease, some may inappropriately secrete PTH and cause hypercalcemia from birth (*CaSR*), whereas others may require additional genetic changes (second hits) to produce clones of cells that eventually secrete enough PTH to cause hypercalcemia. The frequency of these incremental genetic changes likely influences the risk of developing PHPT.

Preoperative detection of genetic disease is important. MEN 1 patients are likely to have associated endocrinopathies, including pancreaticoduodenal, pituitary, thymic tumors, and occasional bronchial carcinoids that can also be treated at the time of parathyroidectomy. HPT-JT probands also benefit from early detection and treatment of renal cysts, adult Wilm's tumor, and uterine carcinoma.

Operative procedures for hereditary patients

The traditional paradigm of adenoma vs multigland disease dictates to either resect the adenoma or debulk enough hyperplastic tissue to achieve normocalcemia. This works well for sporadic PHPT where surgical failures are usually due to persistent disease caused by not resecting ectopic tumors or leaving supernumerary glands in situ. Recurrent disease, defined as redevelopment of hypercalcemia more than 6 months postparathyroidectomy, after initially achieving normocalcemia, is uncommon in sporadic PHPT.

This paradigm does not work well in hereditary PHPT. Conceptually, a surgical "cure" for patients with a genetic predisposition for PHPT is only attainable after complete removal of all parathyroid tissue, with resultant permanent hypoparathyroidism. Any operation less than a total parathyroidectomy will leave abnormal parathyroid tissue at risk for recurrent disease. Therefore, the surgical strategy for hereditary PHPT is pragmatic; the extent of resection is dictated by a compromise to achieve long-term eucalcemia without permanent hypoparathyroidism (a "Goldilocks operation," not too much and not too little). Instead of a simple surgical "cure," the goals of surgery for patients with hereditary PHPT are to achieve normocalcemia for as long as possible, avoid permanent hypoparathyroidism, minimize surgical complications, and facilitate reoperations (48). In addition, because these genetic conditions are rare, there are few high-level evidence-based recommendations to guide surgical treatment (54). What is routinely recommended should be modified in accordance with the patient's desire and the surgeon's experience.

Multiple endocrine neoplasia 1

The most commonly recommended initial operation for MEN 1 patients with PHPT is a subtotal parathyroidectomy, removing 3½ glands and leaving a viable 30- to 50-mg remnant from the most normal-appearing gland that is biopsy confirmed and marked with a suture or a clip (48, 54–56). Concurrent bilateral cervical thymectomy is recommended because of a 15% chance of finding parathyroid tissue in the cervical thymus and because thymic carcinoid tumors occur in this population (57). Another option in the MEN 1 patient is a total cervical parathyroidectomy, cervical thymectomy, and parathyroid autograft to a forearm muscle. The advantage of complete cervical parathyroidectomy is to theoretically eliminate the possibility of recurrent disease in the neck (58, 59).

The multi-institutional French and Belgian GENEM study of 256 patients with MEN 1 showed that since 1990, the majority (51%) of patients underwent subtotal parathyroidectomy. After operation, 19% had persistent disease, and 15% had postoperative hypocalcemia (60). The DutchMEN1 study of 73 MEN 1 patients with long-term postoperative follow-up showed the rate of persistent or recurrent PHPT to be 53% after less than subtotal parathyroidectomy, 17% after subtotal parathyroidectomy, and 10% after total parathyroidectomy with autotransplantation. Postoperative hypoparathyroidism $\geq$ 6

months occurred in 24% of patients after less than subtotal parathyroidectomy, in 39% after subtotal parathyroidectomy, and in 66% after total parathyroidectomy with autotransplantation (61).

Total parathyroidectomy with autotransplantation to the forearm musculature is a more aggressive option with a higher risk of permanent hypoparathyroidism and a potential, but not proven, lower risk of recurrent PHPT. The potentially easier reoperations to find and resect regrown autografts from the muscle of the forearm, vs remnant regrowth in the neck, may not offset the higher risk of permanent hypoparathyroidism. In addition, patients with parathyroid autografts to the forearm are at risk for simultaneous cervical and forearm recurrence that can be difficult to differentiate.

The least aggressive option is single-gland resection with minimal neck exploration (MIP, or focused-targeted-limited parathyroidectomy guided by preoperative localization studies and intraoperative PTH monitoring). A significant proportion of patients with MEN 1 may not have recurrence after resection of only one enlarged gland, and such a recurrence may not occur for many years (62). Accordingly, focused gland resection could be an option in some patients with clear preoperative localization studies showing one enlarged parathyroid gland. The risk for persistent or recurrent disease will no doubt be higher and likely to occur sooner compared to patients who had undergone a subtotal parathyroidectomy. An intermediate option is "unilateral neck clearance." Both glands from the ipsilateral neck as well as the cervical thymic horn are resected, with the expectation that if reoperation is required, it will be limited to the contralateral virgin neck. This approach, however, risks removal of the most normal-appearing gland that may have been the optimal gland to leave as a remnant.

Recent preliminary findings from the DutchMEN1 study suggested genotype-phenotype correlations for the manifestation of PHPT in MEN 1 patients. After less than a subtotal parathyroidectomy, patients with nonsense or frameshift mutations in exons 2, 9, and 10 had a significantly lower risk of persistent or recurrent PHPT compared to those with other mutations (61). Thus, genotyping may be useful in the future to guide the extent of initial parathyroidectomy for patients with MEN 1.

Reoperations for recurrent hyperparathyroidism in MEN 1 usually involve limited exploration to avoid the higher risk of recurrent laryngeal nerve injury in a scarred neck. Reoperations are guided by prior operative and pathological findings and the results of preoperative localization studies. Preoperative laryngoscopy is essential to assess symptomatic or asymptomatic vocal cord paralysis. Cryopreservation of resected parathyroid tissue should be considered for reoperations (57).

Multiple endocrine neoplasia 2A

In contrast to patients with MEN 1, those with MEN 2A are less likely to develop PHPT and even less likely to develop recurrent disease. MEN 2B (MEN 3) is not associated with PHPT. The recommended initial parathyroid operation for MEN 2A patients is to resect only enlarged parathyroid glands (46, 48, 56, 63). MEN 2A patients will also develop C-cell hyperplasia and medullary thyroid cancer; the timing and aggressiveness of medullary thyroid cancer depends on the specific mutation (genotype-phenotype correlation). Thus, all MEN 2A patients will require a total thyroidectomy either to treat clinical disease or for prophylaxis after genetic screening. Parathyroidectomy in MEN 2A patients is often performed at the time of total thyroidectomy. During this exploration, the strategy used in sporadic PHPT will suffice, ie, resecting abnormal-appearing glands, avoiding injury to normal-appearing glands, and documenting their location.

Recurrent PHPT in MEN 2A is rare. Some patients may require a parathyroidectomy in a reoperative neck because MEN 2A was not recognized at the initial thyroid operation or because they develop metachronous PHPT at a later date. Such reoperations should be treated like reoperative parathyroidectomy in patients with sporadic PHPT. Reoperative parathyroidectomy requires preoperative laryngoscopy and localization study-guided focused parathyroidectomy (cryopreservation should be considered). Before exploring patients with MEN 2A, the presence of pheochromocytoma must be ruled out by demonstrating normal levels of plasma free metanephrines or normal 24-hour urinary fractionated metanephrines. α-Adrenergic receptor blockage and adrenalectomy for pheochromocytoma take precedence over parathyroidectomy and thyroidectomy.

Multiple endocrine neoplasia 4

MEN 4 has recently been described where heterozygous germline mutations on the *MEN 1* gene are identified in approximately 70% of patients with a recognized familial syndrome (64). The remaining 30% have a similar phenotype but do not have a detectable mutation. Mutations of other genes such as *CDNK1B* may be involved in the pathogenesis of MEN 4. At least nine cases of MEN 4 have been reported, and eight of the patients with PHPT were treated with either single parathyroid excision or subtotal parathyroidectomy.

Hyperparathyroidism-jaw tumor

Patients with the HPT-JT mutation are at risk for developing both parathyroid cancer and parathyroid "ade-

nomas." Because this syndrome is rare, it is usually suspected only after the patient has already undergone a parathyroidectomy, usually for cancer. These patients present for surgery either after genetic screening or due to symptomatic disease. When symptomatic, patients generally have marked hypercalcemia, unusually large often cystic parathyroid glands, parathyroid carcinomas, or ossifying jaw fibromas. Alternatively, patients present as a family member from a known kindred having undergone biochemical and genetic screening. Parathyroid cancer is suspected clinically when a hyperparathyroid patient has a large, palpable tumor and severe hypercalcemia. Intraoperatively, parathyroid cancer can sometimes be recognized by an unusually hard fibrotic infiltrative gland with local adhesions especially to the thyroid, despite not having had a prior neck operation. When suspected, the cancer should be resected with a concurrent thyroid lobectomy including any invaded muscles (65–67). Recurrences are common. The differential diagnoses in recurrent disease include local cancer recurrence, development of a new "adenoma" or cancer (both treated with repeat resection, if possible), or systemic metastasis (treated with cinacalcet and perhaps chemotherapy). Some surgeons recommend subtotal parathyroidectomy in patients with known HPT-JT syndrome, but high-level evidence is lacking (54). The French national study suggests that *HRPT2/CDC73* deletion mutations may be underdiagnosed (67, 68) and should therefore be screened for in high-risk patients.

Familial hypocalciuric hypercalcemia

FHH patients rarely require surgical intervention. FHH should always be considered, especially in young asymptomatic patients with a low urinary excretion of calcium. There may be an associated family history of failed parathyroid surgery. FHH patients may present in childhood with slightly raised serum PTH and calcium levels. They have a parathyroid and renal calcium set-point disorder due to heterozygous inactivation of the *CaSR* gene (69). FHH_1 is the most common form of FHH and is due to inactivating mutations in the coding sequences of the extracellular *CaSR*. FHH_2 and FHH_3 are due to loss of function mutations in the G protein α-subunit 11 (GNA11) (70) and in adaptor protein 2 σ-1 (71). All forms of FHH are rare (approximately 1 per 1 million), whereas mild PHPT is relatively common, with a prevalence as high as 5.1% in Swedish women (72). Screening for FHH_2 and FHH_3 is not routine because genetic tests are generally not available. FHH patients may have a low 24-hour urinary calcium (typically < 100 mg) and a calcium/creatinine clearance ratio that is usually < 0.01. In contrast, patients with PHPT generally have a 24-hour urinary calcium excretion > 125 mg and a calcium/creatinine clearance ratio > 0.02 (69, 73). These criteria are ascertained in subjects with normal calcium intake because calcium intake may affect urinary calcium excretion. However, overlap occurs especially with elderly patients with PHPT who can demonstrate a ratio < 0.01, possibly due to vitamin D deficiency, slight renal impairment, or lithium use (36, 69, 73). Similarly FHH patients may have urinary calcium levels in the normal range (73). Because of this overlap, it is often helpful to perform genetic screening to detect a *CaSR* mutation that can be detected in 70% of FHH patients. FHH should always be considered in children with hypercalcemia, especially those below age 10. In addition, 50% of FHH patients have an elevated serum Mg level, whereas MEN 1 patients generally present in the second decade of life with a normal serum Mg level. A detailed family history and blood samples from relatives can help discriminate FHH from other causes of hypercalcemia. Most FHH patients are asymptomatic and do not require parathyroid surgery. However, there are cases of FHH patients or kindreds with marked hypercalcemia, high PTH, and parathyroid "adenomas" who appear to benefit from parathyroidectomy (35, 36, 69, 73).

Localization studies and intraoperative PTH assay for familial HPT

Preoperative localization studies have been used to help focus the dissection and guide the extent of resection in patients with familial PHPT (48, 54). These are mandatory for reoperations and are helpful during initial exploration if the surgeon and the patient opt for less than bilateral exploration.

Similar to sporadic PHPT, both localization studies and intraoperative PTH monitoring are more accurate for patients with a solitary lesion. In one series of 28 patients with FIHPT, 68% had multiple gland disease, but sestamibi scans failed to identify multigland disease in 52% (49). Another study showed that although sestamibi scans were not useful for first-time reoperation when the location of the remnant is known, they were very accurate for subsequent reoperations for a supernumerary gland (74). Others have found that less than subtotal parathyroidectomy may be considered in patients with familial PHPT using preoperative localization studies and intraoperative PTH monitoring (75). In one study of 15 patients with FIHPT, who underwent limited operation guided by intraoperative PTH, 14 of 15 had a single gland excision with a surgical success rate of 93% (41).

Clinical suspicion for hereditary PHPT

Not all patients with hereditary PHPT are recognized before their initial operation, especially if there is no family

history of disease. Patients at higher risk of having multigland disease and possible hereditary PHPT include young patients, those with negative preoperative localization studies, and those who had a failed parathyroidectomy. Genetic testing and biochemical screening are recommended for young patients with PHPT and in all patients with newly diagnosed multigland disease (35, 36). Ideally, when indicated, genetic testing should be performed preoperatively because the results could impact surgical intervention.

In some studies, young patients (≤45 y of age) were more likely to have occult hereditary forms of PHPT. In one study, where 136 of 1161 patients were 45 or younger, the prevalence of familial PHPT in young patients was 24% (24 of 102) (6). Two-thirds (16 of 24) were clinically diagnosed, and one-third (eight of 24) were occult and were only diagnosed after genetic testing. Of these 24 patients with familial PHPT, there were 15 with MEN 1, four with *RET*, three with *CaSR*, and two with *HRPT2/CDC73* mutations. Of the eight patients with occult familial PHPT, there were four with MEN 1, three with *CaSR*, and one with a *HRPT2/CDC73* mutation (6). Other studies found that occult familial PHPT is not common in young patients who can be managed with the same approach as those presenting with sporadic PHPT of any age (76). In this study of 1253 patients, 87 were younger than 40; the prevalence of MEN 1 was 13% in these younger patients. Of the 33 patients who consented to genetic study, 12 (10 MEN 1, two MEN 2A) were clinically diagnosed (by syndromic findings or family history) before surgery. Of the other 21 patients without known familial PHPT, 12 underwent conventional bilateral exploration, and nine had focused endoscopic parathyroidectomy. Nineteen patients (91%) had uniglandular disease, and all were cured. Only one of the 21 patients (4.7%) was found to have occult MEN 1 by genetic testing and had "double adenomas" excised (76).

10) What are the complications of parathyroid surgery?

When parathyroid surgery is performed by experienced surgeons, the mortality rate approaches 0% in the vast majority of series. However, one study reported a mortality rate of 10% in elderly patients and was attributed to comorbid conditions (77). The overall combined perioperative morbidity rate is less than 4% in most reported series. This rate may be higher in elderly patients, especially if general anesthesia is employed and prolonged hospitalization is required. Recurrent laryngeal nerve injuries are reported to be $< 1\%$. Subtle injuries involving the external branch of the superior laryngeal nerve are difficult to confirm and are less likely to be reported. Symptomatic postoperative hypocalcemia can prolong hospitalization and result in readmission. Moderate postoperative hypocalcemia is common, occurring in 15–30% of patients, is usually transient, and is generally managed in the outpatient setting. Postoperative hungry bone syndrome is unusual in asymptomatic patients but is more likely to occur if the patient has elevated serum alkaline phosphatase activity noted on preoperative evaluation. Many surgeons routinely employ oral calcium supplementation in the early postoperative period to minimize the incidence of symptomatic hypocalcemia. A randomized trial comparing traditional bilateral cervical exploration with MIP demonstrated that MIP was associated with a lower incidence of transient postoperative hypocalcemia (78). Wound complications including infections are rare. Postoperative cervical hematomas are extremely rare, but can cause life-threatening airway obstruction. However, the vast majority of patients have an uncomplicated perioperative course.

11) What are the conclusions?

There have been major advances in the surgical management of patients with PHPT. The operations are extremely safe and curative outcomes are achieved in the vast majority of patients when the operations are performed by experienced surgeons. Minimally invasive techniques are appropriate for most patients. These techniques require adequate imaging, experienced surgeons, and employment of an intraoperative PTH assay. However, these techniques are not appropriate for a significant number of patients who have multigland disease, especially those who have familial forms of PHPT. The probability that an apparent sporadic patient actually represents a familial case appears to be between 5 and 10%. Because these patients generally have asymmetric hyperplasia, they can be confused with a patient who has a single parathyroid adenoma and can be subjected to an inadequate operation. Accordingly, during the preoperative evaluation, it is critical to obtain a detailed family history and employ genetic screening in patients who appear likely to harbor familial disease. The extent of genetic testing will vary depending on resources and the index of suspicion. When familial syndrome screening is done, we recommend testing for MEN 1, MEN 2, FHH_1, and the HPT-JT syndrome. These include young patients, those with a family history of related endocrinopathies, and those who are found to have multigland disease.

Parathyroid imaging is not a diagnostic procedure and should only be performed in patients who plan to undergo parathyroid surgery. Imaging is performed as a localization procedure to allow the surgeon to design an individualized and appropriate operation. Ideally, it is the sur-

geon in concert with the radiologist and nuclear medicine physician who should select the imaging studies because it is the surgeon who must decide if they are of adequate quality and sensitivity to plan for an operation. Negative or discordant imaging should never preclude referral to an endocrine surgeon, and noninformative imaging is not an indication for nonoperative management of PHPT.

Patients with PHPT who meet surgical criteria should be referred to an experienced endocrine surgeon to discuss the risks, benefits, and potential complications of surgery. Patients who do not meet surgical criteria and in whom there are no medical contraindications to surgery may request a visit with an experienced endocrine surgeon. Alternatively, a multidisciplinary endocrine conference with surgeon involvement could be employed to address relevant issues.

12) What are the future directions?

A randomized prospective collaborative trial will be required to demonstrate whether surgery is appropriate for virtually all "asymptomatic" patients with PHPT. Such a study would randomize all patients who do not have a clear indication for parathyroidectomy to either surgery or nonoperative management. It would include all patients willing to participate who are referred to either their participating endocrinologist or surgeon. This study would also include investigating the effects of surgical treatment on end-organs including the bones, kidney, and brain (neurocognitive). One could also employ such a trial to obtain serial blood and urine samples to measure select markers of bone turnover and remodeling.

The definition of an experienced endocrine surgeon is imprecise. The term should be explicitly defined based on the best available data. The volume-outcome relationship for parathyroid surgeons requires additional investigation in concert with defining institutional-volume outcome relationships. Prospective and verified databases would improve endocrine data analysis and form the basis for quality improvement.

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