Surgical Management of Primary Hyperparathyroidism: State of the Art

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- Primary hyperparathyroidism
- Parathyroid hormone
- Preoperative localization
- Intraoperative parathyroid hormone monitoring
- Focused parathyroidectomy
- Bilateral neck exploration

HISTORY OF PARATHYROID SURGERY

...It seems hardly credible that the loss of bodies so tiny as the parathyroids should be followed by a result so disastrous.

—William S. Halsted, 1907

Discovery of the Parathyroid Glands

The parathyroid glands were first identified by Sir Richard Owen in 1850 during an autopsy of an Indian Rhinoceros acquired by the Zoological Society of London. In the 1880s, a Swedish medical student from Uppsala, Ivor Sandstrom, first described the glandulae parathyroideae in humans including their gross anatomic and microscopic features. It is remarkable that the elusive function of the parathyroid glands was appreciated before the anatomic discovery of these glands themselves; the association of postoperative tetany in patients after total thyroidectomy was first made by Anton Wolfer in 1879. More than a decade later, Parisian physiologist Eugene Gley recognized the loss of parathyroid glands caused tetany in 1891 after conducting selective parathyroidectomy in dogs. His observations, however, did not recognize the intimate association between the parathyroid glands and calcium homeostasis. In 1906, Jacob Erdheim identified enlarged parathyroid...
glands that he concluded compensatory in several patients with bone disease. This relationship between the parathyroid glands and calcium was definitively demonstrated in 1909 by William MacCallum and Carl Voegtlin, who corrected clinical tetany in dogs by the administration of either parathyroid extract or exogenous calcium. Although Max Askanazy first published the account of solitary parathyroid tumors in association with von Recklinghausen disease of bone in 1903 (osteitis fibrosa cystica), in 1915 Friedrich Schlagenhauer unequivocally suggested that single parathyroid tumors were the primary cause of bone disease in 2 patients with osteomalacia, and recommended such tumors be surgically excised in similar patients with von Recklinghausen disease of bone.

The First Operations for Hyperparathyroidism

Ten years would pass before Schlagenhauer’s treatment recommendations for hyperparathyroidism would be followed. Felix Mandl performed the first parathyroidectomy in 1925 on Albert Jahne, a 34-year old Viennese tram car conductor. After Jahne had been unsuccessfully treated with parathyroid extract and tissue implantation, Mandl excised an enlarged parathyroid gland that in retrospect may have represented a parathyroid carcinoma. The operation was initially successful, and altered the practice dogma for treatment of hyperparathyroidism at that time. However, Jahne’s condition recurred, and he died soon after a second unsuccessful operation. In 1926, EJ Lewis performed the first parathyroidectomy in the United States at Cook County Hospital in Chicago on a 29-year old woman with parathyroid carcinoma who required multiple reoperations. A few months later, comprehensive surgical management of hyperparathyroidism would be learned through merchant marine captain Charles Martell, who underwent 7 operations by Oliver Cope and others in Boston and New York for his condition. Martell was eventually found to have a mediastinal parathyroid adenoma, but unfortunately died 6 weeks later as a consequence of his disease and its treatment. In 1928, Issac Olch performed the first successful parathyroidectomy at Barnes Hospital in St. Louis on Elva Dawkins, who underwent excision of a solitary enlarged parathyroid gland. Physicians from this institution involved in the care of Dawkins would later define the term “hyperparathyroidism” in an article published in 1929, describing associated bone findings as well as muscle weakness, renal stones, high serum calcium, and elevated urine calcium excretion.

Parathyroid Hormone and the Development of Immunoassays

To further elucidate the function of the parathyroid glands, and facilitate diagnosis and therapy, Adolf Hanson, a general surgeon from Faribault, Minnesota, and James Collip, a Canadian biochemist, separately purified parathyroid extract in 1923 and 1925, respectively, to treat tetany, hypoparathyroidism, and osteoporosis. Furthermore, Collip also worked to make this parathyroid hormone (PTH) commercially available. In 1963, Solomon Berson and Rosalyn Yalow developed a radioimmunoassay for PTH. In 1977, Yalow received the Nobel Prize for discovery of this PTH assay and its application to measuring other peptide hormones. In 1968, Eric Weiss and Janet Canterbury identified bovine crossover antibodies to human PTH, and they later developed a radioimmunoassay that measured the C-terminal and mid-molecule of the hormone. In 1987, Samuel Nussbaum and colleagues developed a highly sensitive 2-site antibody immunoradiometric assay (IRMA) for measuring intact PTH. Later the same year, Richard Brown and colleagues from Wales reported measuring circulating intact (1–84) PTH with a 2-site immunochromeluminometric assay (ICMA) that demonstrated the 5-minute half-life of intact PTH with a specificity to
distinguish between patients with elevated PTH levels and hypercalcemia of malignancy. From these scientific discoveries, George Irvin applied and refined such techniques to routine clinical practice in the surgical management of primary hyperparathyroidism at the University of Miami. In 1990, Irvin measured intraoperative PTH levels using IRMA to confirm complete removal of hypersecreting parathyroid glands and predict curative resection in a reoperative patient with an intrathyroidal parathyroid adenoma not appreciated at initial exploration. With excellent results and applicability to the outpatient setting, Irvin popularized this approach of limited or “focused” parathyroidectomy by combining preoperative localization studies and rapid intraoperative PTH monitoring (IPM) for the treatment of patients with primary hyperparathyroidism.

Evolution of Parathyroid Surgery

With recent advances that include preoperative parathyroid localization with Sestamibi ± single-photon emission computed tomography (SPECT) or ultrasound (US) with rapid IPM, limited or “focused” parathyroidectomy performed through a small cervical incision serves as an attractive alternative to conventional bilateral cervical exploration (BNE) for primary hyperparathyroidism. Parathyroid localization by imaging studies is an important prerequisite for successful focused neck exploration. Operative success rates are further improved by IPM before and after removal of all abnormal parathyroid glands. When intraoperative PTH levels are reduced by more than 50%, successful exploration is assured with a predictive cure of at least 95% or greater. Advantages of focused parathyroidectomy in the ambulatory setting include improved cosmetic results with smaller incisions, decreased postoperative pain, shorter operative time, decreased hospitalization, and rapid postoperative recovery with greater than 95% cure rate comparable to BNE. Other recent surgical options for the treatment of patients with primary hyperparathyroidism include radioguided, endoscopic, and video-assisted parathyroidectomy.

SURGICAL ANATOMY, EMBRYOLOGY, AND PATHOLOGY OF THE PARATHYROID GLANDS

Normal parathyroid glands present in varied shapes and sizes. When subscapular at the upper thyroid pole, parathyroid glands may appear flattened. At the cricothyroid junction or thymic tongue, such glands may resemble oval, spherical, or teardrop shapes. Most parathyroid glands are yellow-tan or reddish in color depending on fat content, number of oxyphilic cells, and degree of vascularity. The average parathyroid gland measures 5 mm at greatest dimension with an average weight ranging from 30 to 40 mg. Composed of chief and oxyphilic cells, parathyroid glands also consist of adipose tissue and fibrovascular stroma. Found in both children and adults, chief cells that predominantly contain lipids are usually involved in hypersecretory processes. In hyperparathyroidism, the amount of lipid within chief cells of the gland is significantly diminished. Oxyphilic cells that characteristically have granular cytoplasm are primarily found in adults.

Successful parathyroidectomy is inextricably related to the understanding of the anatomic and embryologic relationship of the parathyroid glands to the thyroid gland and thymus. Most humans typically have 4 parathyroid glands. Studies on human cadavers reveal 84% have 4 parathyroid glands, 13% have 5 or more (supernumerary) glands, and 3% of individuals have only 3 parathyroid glands. Supernumerary glands that most often reside in the thymus are of clinical significance in patients with parathyroid hyperplasia associated with secondary, tertiary, and familial hyperparathyroidism. At 4 weeks of embryologic development, the superior parathyroid
glands originate from the fourth branchial pouch undergoing very little migration, whereas the inferior parathyroid glands descend from the third branchial pouch to more varied locations along with the thymus.\(^{27}\) The paired superior and inferior parathyroid glands are typically symmetric in location bilaterally. In about 80% of cases, the superior and inferior parathyroid glands receive their blood supply from the inferior thyroid artery.

The superior parathyroid glands are usually located on the posteromedial aspect of the superior poles of the thyroid gland about 1 cm above the intersection of the recurrent laryngeal nerve and inferior thyroid artery at the level of the cricoid cartilage. The superior glands are typically posterior and superior to the recurrent laryngeal nerve. Because they undergo less embryologic migration during development, the location of the superior glands is more constant and they are seldom found in ectopic positions. If ectopic, these glands are usually found in the tracheoesophageal groove, posterior mediastinal, retroesophageal, retropharyngeal, or intrathyroidal locations.

The inferior parathyroid glands are located on the posterolateral surface of the inferior poles of the thyroid gland below the intersection of the recurrent laryngeal nerve and inferior thyroid artery. Unlike the superior glands, the inferior glands are seldom subscapular and they are usually located anterior to the recurrent laryngeal nerve. Because these glands extensively migrate with the thymus during embryologic development, they may widely vary in distribution. About 80% of inferior parathyroid glands may reside anteriorly, inferiorly, or laterally within 2 cm of the inferior pole of the thyroid gland.\(^{28}\) These glands may also be found in ectopic locations most commonly within the true sheath of the thymus (15%), and less frequently, in an intrathyroidal location (1%–4%), anterior mediastinum, submandibular location, tracheoesophageal groove, retroesophageal space, and carotid sheath.\(^{28}\) The surgically excised thymus and these other sites should be examined carefully at the time of initial exploration when abnormal parathyroid glands are not found in orthotopic locations.

Primary hyperparathyroidism, resulting from the overproduction of PTH by one or more hyperfunctioning parathyroid glands, can be caused by 3 different pathologic lesions. Parathyroid adenoma is a benign encapsulated tumor that accounts for most cases (85%–96%) of primary hyperparathyroidism. Although most have a single affected gland, 2% to 5% of patients with primary hyperparathyroidism may have 2 affected glands (“double adenoma”) with the remaining glands appearing normal. Parathyroid hyperplasia is caused by an increase of parenchymal mass within all the parathyroid glands, and it accounts for 4% to 15% of cases. The incidence of hyperplasia increases in patients with multiple endocrine neoplasia (MEN) type 1 and 2, and non-MEN familial isolated hyperparathyroidism (FIHPT). Parathyroid hyperplasia is treated either by subtotal (3.5) parathyroidectomy or total parathyroidectomy with autotransplantation. For patients with MEN, cervical thymectomy should also be performed. Parathyroid carcinoma is an indolent growing malignant tumor of parenchymal cells responsible for less than 5% of all primary hyperparathyroidism cases. Because this carcinoma is invasive, parathyroidectomy should be performed with en bloc resection of the ipsilateral thyroid lobe, avoiding parathyroid capsule violation.

**Clinical Presentation and Evaluation**

Primary hyperparathyroidism results from PTH overproduction by one or more hyperfunctioning parathyroid glands, which usually cause hypercalcemia. The widespread use of serum channel autoanalyzers since the 1970s has allowed for earlier diagnosis of primary hyperparathyroidism in patients before the manifestation of clinical symptoms.\(^{29}\) This development along with the aging population in the United States has
led to the reported increased incidence of primary hyperparathyroidism. The most common cause of hypercalcemia in the outpatient setting, the incidence of primary hyperparathyroidism in the general population ranges from 0.1% to 0.3%, occurring more frequently in women than men with advanced age. Known risk factors for primary hyperparathyroidism include abnormalities of the PRAD1, MEN1, and HRPT2 genes that encode for cyclin D1, menin, and parafibromin, respectively, and radiation exposure to the neck, especially during childhood.

The clinical presentation of primary hyperparathyroidism has evolved throughout the years. The classic description of kidney “stones,” painful “bones,” abdominal “groans,” lethargic “moans,” and psychiatric “overtones” are now infrequently encountered in the United States. Today, patients with primary hyperparathyroidism present most commonly with abnormal biochemical results and do not have disease manifestations such as fatigue, musculoskeletal pain, weakness, polyuria, nocturia, memory loss, constipation, polydipsia, heartburn, and depression. Hypertension and nephrolithiasis are the most commonly associated preoperative conditions found in patients with primary hyperparathyroidism. Nonetheless, when properly evaluated, up to 80% of patients currently present with nonspecific symptoms of depression, fatigue, and lethargy, and they often are considered asymptomatic.

Once primary hyperparathyroidism is suspected or hypercalcemia is identified, biochemical confirmation is necessary. Oversecretion of PTH directly stimulates bone resorption, enhances intestinal absorption of calcium, inhibits renal calcium excretion, and indirectly stimulates the production of active vitamin D that also promotes intestinal calcium absorption. The negative feedback that controls PTH secretion is affected in primary hyperparathyroidism, resulting in inappropriate autonomic secretion of PTH concomitant with hypercalcemia. Diagnosis of primary hyperparathyroidism is made by demonstrating elevated total serum or ionized calcium levels, and high intact PTH levels in the setting of normal renal function. In primary hyperparathyroidism, vitamin D metabolism is typically characterized by low plasma levels of 25-hydroxyvitamin D, and high plasma levels of 1,25-dihydroxyvitamin D. Twenty-four-hour urine calcium collection is also helpful to exclude the diagnosis of benign familial hypocalciuric hypercalcemia (BFHH). A rare condition identified in patients with a family history of hypercalcemia and decreased urine calcium excretion since birth, BFHH biochemically mimics primary hyperparathyroidism with elevated calcium and PTH levels, but with low levels of urinary calcium (less than 100 mg/24 h). Similarly, the urinary calcium-to-creatinine (Ca/Cr) clearance ratio in BFHH is less than 0.01, whereas in patients with primary hyperparathyroidism the ratio is greater than 0.02. An autosomal dominant disease, BFHH is a benign condition that cannot be corrected by parathyroidectomy.

Patients may also present with normocalcemic hyperparathyroidism. Most of these patients have primary hyperparathyroidism with normal calcium and elevated PTH levels after appropriate diagnostic evaluation. This condition is generally recognized in patients being evaluated for osteoporosis. In some individuals, this may be the earliest presentation of symptomatic primary hyperparathyroidism, whereas in others it may represent PTH elevation secondary to vitamin D deficiency or renal dysfunction. Patients occasionally present with hypercalcemia and inappropriately normal PTH level, and many will have hyperparathyroidism after further workup. Nevertheless, surgeons treating hyperparathyroidism should be knowledgeable about these varied presentations to avoid poor surgical outcomes. Other causes of hypercalcemia that also need to be excluded include underlying malignancy, excessive thiazide diuretics, lithium, vitamin A or D excess, milk-alkali syndrome, sarcoidosis, Paget disease, or prolonged immobilization.
Although not required for diagnosis, dual-energy x-ray absorptiometry (DEXA) may be useful in the measurement of bone mineral density (BMD) in patients with primary hyperparathyroidism. Because many have decreased BMD secondary to this condition, most patients with primary hyperparathyroidism should undergo DEXA testing. If osteoporosis is documented (T-score less than −2.5), parathyroidectomy should be strongly considered. In primary hyperparathyroidism, bone density losses are greater in areas of cortical bone such as the femoral neck and radius, but can occur at all bony sites. The benefit of parathyroidectomy can be more pronounced at the hips because of the morbidity and mortality associated with bone fracture at these sites.

INDICATIONS FOR PARATHYROIDECTOMY

Although symptomatic primary hyperparathyroidism remains a clear indication for surgical treatment, there remains some controversy among clinicians regarding the indications for performing parathyroidectomy in asymptomatic patients. The efficacy of parathyroidectomy in asymptomatic patients has been questioned due to the indolent nature and less understood natural history of primary hyperparathyroidism. To address this issue, the National Institutes of Health (NIH) convened a consensus conference in 1990, and another workshop in 2002 to establish guidelines for the surgical management of asymptomatic patients that include: serum calcium level 1.0 mg/dL or greater above the accepted normal range; 24-h urinary calcium excretion greater than 400 mg/d; creatinine clearance reduced by 30%; T-score less than −2.5 at any site; and age younger than 50 years. Parathyroidectomy was also recommended in patients for whom medical surveillance is either undesirable or impossible.41 Many clinicians believe that the NIH criteria for asymptomatic patients are too conservative, with many experienced endocrine surgeons basing the operative decision not only on these objective criteria but on subjective complaints as well.42 Others believe that these criteria fail to address the role of neurocognitive deficits in patients with primary hyperparathyroidism, with several studies showing improvements of depression, anxiety, sleep disturbances, poor memory, and cognitive impairment after parathyroidectomy.43 Recent evidence from a long-term study of primary hyperparathyroidism over 15 years suggests the NIH guidelines for parathyroidectomy do not reliably predict worsening disease progression in asymptomatic patients.44 Because meeting surgical NIH guidelines at the time of diagnosis did not predict a worse outcome of bone disease in patients who did not undergo parathyroidectomy, this report raises questions as to whether the guidelines for surgery in asymptomatic patients with primary hyperparathyroidism are appropriate for clinical decision making. Nonetheless, it is the opinion of the article authors (J.I.L., C.C.S.) that all “asymptomatic” patients with clear biochemical diagnosis of primary hyperparathyroidism should be offered a surgical consultation with an experienced parathyroid surgeon.

PREOPERATIVE PARATHYROID LOCALIZATION

The only localization that a patient needs who has primary hyperparathyroidism is the localization of an experienced surgeon!

—John L. Doppmann, 199145

An important advancement in the surgical treatment of primary hyperparathyroidism has been the improved preoperative localization of hyperfunctioning parathyroid glands using a variety of imaging techniques including sestamibi-technetium 99m
scintigraphy (sestamibi), ultrasonography (US), and 4-dimensional computed tomography (4D-CT). Sestamibi, especially combined with SPECT, is considered the best single study for preoperative parathyroid localization.\(^{46,47}\) However, US has recently been used more frequently, and it has been shown to be accurate and cost-effective in distinguishing enlarged parathyroid glands from surrounding structures.\(^{48-50}\) Although either study can adequately localize abnormal glands alone in many patients, both studies can be used concordantly, significantly improving preoperative localization for successful focused parathyroidectomy.\(^{51-54}\) For patients undergoing reoperative exploration for recurrent or persistent parathyroid disease, 4D-CT may have an important role in preoperative gland localization.\(^{55}\)

Sestamibi scintigraphy has played a key role in the acceptance of more limited approaches to the surgical treatment of primary hyperparathyroidism. Sestamibi is avidly retained by parathyroid adenomas thought to be secondarily related to the high mitochondrial content of this tissue. Sestamibi can localize 80% to 90% of single abnormal parathyroid glands, but it is less sensitive in the diagnosis of multiglandular disease (MGD).\(^{56-58}\) The specificity of sestamibi scanning can be improved with delayed (2-hour) planar and multidimensional imaging obtained by SPECT.\(^{59,60}\) Although there are no significant differences in the sensitivity of the varied types of sestamibi scanning used to identify abnormal gland(s), multidimensional imaging (ie, SPECT) provides additional information regarding the anatomic location of these glands in many patients.\(^{51}\) Although its sensitivity for MGD is low, misdiagnosis can be avoided with supplemental preoperative imaging or intraoperative PTH measurements.\(^{57,58,62}\) The coexistence of thyroid nodules or lymph nodes that can mimic abnormal parathyroid glands may also cause false-positive results on sestamibi scans. Such results can be minimized by combining sestamibi with neck US to distinguish between thyroid lesions and enlarged parathyroid glands or by the combined use of SPECT that can provide simultaneous 3-dimensional functional and anatomic information delineating thyroid and parathyroid lesions.\(^{46,47}\) Sestamibi-SPECT is particularly useful in detecting smaller parathyroid lesions that may reside posterior the thyroid gland (Fig. 1).

In recent years, US has been more commonly used for preoperative parathyroid localization. This imaging modality can be very accurate by providing important anatomic information delineating an enlarged parathyroid gland from surrounding structures with 70% to 80% accuracy.\(^{48-50}\) This noninvasive imaging modality is inexpensive, but has a varied sensitivity in the localization of abnormal parathyroid glands. Furthermore, US is operator dependent with limited application to the neck for parathyroid localization because it cannot identify glands in the mediastinum. At the authors’ institution, US is routinely performed by endocrine surgeons (J.I.L., C.C.S.) in the clinical setting. Surgeon-performed ultrasound (SUS) enables clinicians who best appreciate neck anatomy to obtain real-time information regarding the anatomic location of enlarged parathyroid glands among several other structures, and allows for evaluation of thyroid abnormalities that may require surgical treatment (Fig. 2). Several studies demonstrate that preoperative SUS localizes enlarged parathyroid glands similar to sestamibi with improved sensitivity over radiologist-performed ultrasound.\(^{48-50}\) Like sestamibi, US has a lower sensitivity for MGD. The overall sensitivity of dual-phase \(^{99m}\)Tc sestamibi scintigraphy in comparison with US is 88% versus 79% for single adenomas, 30% versus 16% for double adenomas, and 44% versus 35% for multiple-gland hyperplasia.\(^{63}\)

Combined sestamibi and US can increase accuracy of localization of a single adenoma from 94% to 99%. When concordant, sestamibi and US localization has been reported to have an operative success rate approaching 99%, obviating the need for IPM.\(^{51-54}\) Although studies show excellent outcomes in this subgroup of
highly selected patients with concordant localizing studies, this selective approach significantly limits the number of eligible patients for focused parathyroidectomy. Preoperative sestamibi and US have been shown to be concordant only 50% to 60% of the time, leaving a great number of patients with no definitive or discordant localization.\textsuperscript{64} Discordance between sestamibi and US has been reported as high as 38% in consecutive patients treated by parathyroidectomy with an 11% rate of MGD. Although sensitivity for MGD for both localizing studies is lower, missed abnormal glands can be minimized with additional IPM.\textsuperscript{64}

In patients with recurrent or persistent disease, 4D-CT may have a useful role in the localization of abnormal parathyroid glands in conjunction with other imaging studies.
that may sometimes fail. The wash-in and wash-out characteristics of parathyroid glands allow 4D-CT to identify hyperfunctioning glands with improved sensitivity (Fig. 3). Although under current investigation for routine preoperative parathyroid localization, 4D-CT nevertheless remains a useful imaging modality in reoperative patients.

INTRAOPERATIVE PARATHYROID HORMONE MONITORING

When surgeons have the ability to measure endocrine gland function intraoperatively, our dedication to chasing hormones will become a lot easier and much more fun.

—George L. Irvin, 1999

A significant innovation in the surgical treatment of primary hyperparathyroidism, IPM, serves as a surgical adjunct to quantitatively determine the excision of all hyperfunctioning parathyroid tissue. Refined and first implemented routinely by George Irvin at the University of Miami, IPM allows for more limited operations that minimize the need to identify all 4 parathyroid glands. IPM can confirm adequate removal of all hyperfunctioning parathyroid glands and predict operative success with reduced operative time compared with BNE. IPM is possible due to the short half-life (3.5–5 minutes) of PTH. IPM involves the rapid assay measurement of preoperative, preexcision, and postexcision PTH levels at 5 and 10 minutes after removal of all hypersecreting parathyroid glands. Intraoperative criterion for successful and curative parathyroidectomy originally described by Irvin is defined by a decrease of intact PTH levels greater than 50% from the highest preincision or preexcision hormone level in a peripheral blood sample obtained 10 minutes after removal of all abnormal parathyroid tissue. If this criterion is met, the operation is completed and the incision closed. If the 10-minute sample shows an insufficient decrease, further neck exploration is performed. With IPM, hypersecretory activity of parathyroid glands is determined exclusively by measured PTH levels, not by gland size or histology. Patients

Fig. 3. An axial view of a 4-dimensional computed tomogram showing an enlarged parathyroid gland (arrow) located in the retroesophageal space of a patient who underwent 2 prior failed parathyroidectomies.
with more than one hypersecreting parathyroid gland by IPM measurement are determined to have MGD.

An example of IPM in a patient with primary hyperparathyroidism successfully treated following resection of a solitary hypersecreting parathyroid gland is illustrated in Fig. 4. This criterion has been designed to consider the half-life of PTH, and to avoid misleading results caused by spikes in PTH levels that may result from parathyroid gland mobilization. A decline of more than 50% in PTH level from the highest preincision or preexcision level indicates operative success with predictive cure in 97% of cases. Other surgeons, however, use more stringent intraoperative criteria for operative cure of primary hyperparathyroidism. In addition to a greater than 50% reduction of intraoperative PTH level, these proponents additionally require that the final postexcision PTH level falls into normal range before concluding the surgical procedure to lower the incidence of operative failure or persistent hyperparathyroidism due to false-positive results. Recent evidence, however, suggests that patients in whom intraoperative PTH levels decrease more than 50% and do not drop into normal range continue to be biochemically eucalcemic after parathyroidectomy, without an increased incidence of operative failure or recurrent hyperparathyroidism. Each operating surgeon should validate the IPM criteria that maximizes cure and avoids excessive neck exploration at their respective institutions.

In patients with discordant or incorrect concordant preoperative localization studies, IPM remains a useful adjunct that limits exploration and prevents operative failure due to MGD. The rapid P assay is additionally useful when surgeons and pathologists have difficulty distinguishing parathyroid, thyroid, and lymph node tissue. Aspirate of parathyroid tissue diluted in a syringe containing 1 mL saline, and measurement of its contents by rapid assay yields PTH values greater than 1500 pg/mL that confirm diagnosis. When both sestambi and US studies are negative, differential venous PTH sampling measured by rapid assay can be performed to lateralize the hypersecreting gland to one side of the neck. If this test is indeterminate, one side is randomly chosen to be explored first. Operative failure and BNE rates have decreased significantly for initial and reoperative parathyroidectomy with IPM. Failure
rates from initial parathyroidectomy have reportedly decreased by 4.5% after the implementation of IPM. Although variable, IPM has been reported to increase success rates by 10% at initial operation, and by 18% in reoperative patients for failed parathyroidectomy.

FOCUSED PARATHYROIDECTOMY

With the advent of improved preoperative localization techniques, increased availability of IPM, and the predominance of single gland disease in 85% to 96% of patients with primary hyperparathyroidism, limited or focused parathyroidectomy has replaced traditional BNE as the standard approach at many specialized centers worldwide. Attractive advantages of focused parathyroidectomy include improved cosmetic results with smaller incisions, decreased pain, shorter operative time, ambulatory surgery, decreased hospitalization, rapid postoperative recovery, less injury to the recurrent laryngeal nerve, decreased postoperative hypocalcemia, and comparable success rates to conventional BNE. In a survey among members of the International Association of Endocrine Surgeons (IAES), 92% of responding surgeons performed focused parathyroidectomy with small incisions, highlighting the profound worldwide shift in the surgical management of primary hyperparathyroidism over the last decade.

Many techniques of focused parathyroidectomy have been described that incorporate and share common aspects and principles of minimally invasive surgery that result in less dissection, decreased operative time, less morbidity, and comparable reported operative success to BNE ranging from 97% to 99%. In general terms, the procedure is performed in patients with a single parathyroid adenoma localized by preoperative sestamibi or US through a central or lateral incision measuring from 2 to 4 cm. Only the abnormal parathyroid gland is identified and excised. IPM is used by most to confirm that no additional hypersecreting parathyroid tissue remains. When IPM levels decrease by more than 50%, the limited operation is completed. Performed under general or local anesthesia, focused parathyroidectomy can be offered to most patients in the outpatient setting. Patients with known MGD preoperatively are not offered this focused approach.

At the institution where the authors practice, focused parathyroidectomy is usually performed under general or local anesthesia in the ambulatory setting. Before limited exploration performed through a cervical incision measuring between 2 and 4 cm, a peripheral blood sample for a baseline (preincision) PTH level is obtained. After identification of the abnormal parathyroid gland, and just before clamping of its vascular pedicle, a preexcision PTH hormone level is measured followed by subsequent 5- and 10-minute blood samples. Intraoperative criterion for successful parathyroidectomy is defined by a decrease of intact PTH level more than 50% from the highest preincision or preexcision hormone level in a peripheral blood sample obtained 10 minutes after removal of all abnormal parathyroid tissue. If this criterion is met, the neck exploration is completed and the incision closed. If the 10-minute sample shows an insufficient decrease, further neck exploration is performed. Secretory activity of parathyroid glands is determined exclusively by measured PTH levels, and not by gland size or histology. Patients with more than one hypersecreting parathyroid gland measured by IPM are determined to have MGD. Patients are carefully followed in the outpatient setting, with serum calcium, PTH, and vitamin D levels measured at 2 months, 6 months, and yearly thereafter to determine operative outcome. At this institution, operative success is defined as
continuous eucalcemia lasting 6 months or longer whereas recurrent hyperparathyroidism is defined as elevated calcium and PTH levels more than 6 months after successful parathyroidectomy. Operative failure is defined as elevated calcium and PTH levels within 6 months after parathyroidectomy.

**Outcomes**

The success of focused parathyroidectomy has been confirmed by several studies with cure and complication rates that are comparable to traditional BNE. In one study of 656 consecutive patients older than 11 years in which 255 underwent focused parathyroidectomy and 401 conventional BNE, the cure rates were 99% and 97% with complication rates of 1.2% and 3%, respectively. Focused parathyroidectomy also had a reduced operating time of 1.3 hours compared with 2.4 hours for BNE, and a reduction in length of hospitalization of 0.24 days compared with 1.64 days, respectively. In another subsequent study of 718 patients older than 34 years, the cure rates for focused parathyroidectomy and BNE were 97% and 94% with operative failure rates of 3% and 6%, respectively. Patients who underwent focused parathyroidectomy had a 7% lower incidence of MGD compared with BNE group.

Finally, in a 5-year follow-up of a randomized controlled trial, focused parathyroidectomy provided the same long-term results as traditional BNE in patients with primary hyperparathyroidism. The aforementioned studies all concluded that focused parathyroidectomy was a valid and attractive alternative to BNE for most patients with primary hyperparathyroidism.

At present there are minimal long-term data to confirm the durability of operative success from focused parathyroidectomy compared with conventional BNE. Critics of the focused approach predict that the combined use of preoperative localization and IPM lead to a high failure rate due to missed abnormal glands or MGD, risking future disease recurrence. What remains unknown is whether these enlarged parathyroid glands judged to be abnormal by the surgeon that might otherwise have been left alone and never seen during focused operations later become hyperfunctioning glands. In one study of simulated focused parathyroidectomy in 916 patients with primary hyperparathyroidism, preoperative sestamibi and US were used for parathyroid localization and IPM was performed in all patients. Routine BNE was then performed in all these patients, revealing 16% of patients with additional enlarged glands, and raising the concern that the longer-term failure or recurrence rate for focused parathyroidectomy may be higher than reported in early results.

Other reports, however, suggest otherwise, and indicate that focused parathyroidectomy has long-term durability of operative success comparable to BNE. In one study with a mean follow-up of almost 5 years, none of 181 patients cured by image-guided parathyroidectomy developed recurrent disease. In a randomized clinical trial with a 5 year follow-up, the recurrence rates for focused parathyroidectomy and BNE were 5% and 3%, respectively. In yet another analysis from the authors’ institution, only a 3% rate of disease recurrence developed in 164 patients with a mean follow-up of almost 7 years after successful focused parathyroidectomy (John I. Lew and George L. Irvin III, 2009; unpublished results). Many other studies demonstrate that parathyroid size or histopathology do not necessarily correlate with PTH secretion and, therefore, may not be reliable indices in determining abnormal hypersecreting parathyroid glands. These findings together indicate that the focused approach has a durable rate of operative success and does not fail to identify MGD as a cause of recurrent hyperparathyroidism, and strongly suggest that normal secreting, variously sized parathyroid glands left in situ do not contribute to higher long-term failure or recurrence rates.
BILATERAL NECK EXPLORATION

The traditional standard approach in the surgical treatment of primary hyperparathyroidism, BNE requires the identification and careful examination of usually 4 parathyroid glands. When performed by experienced surgeons, the operative cure rate for BNE is more than 95% with a complication rate ranging from 1% to 4%. There are certain clinical conditions in which BNE is preferred over focused parathyroidectomy. BNE is indicated for cases of MEN and non-MEN FIHPT wherein there is a higher incidence of MGD than single-gland disease. Lithium-associated hyperparathyroidism is another condition in which BNE is preferable due to its higher incidence of MGD. When patients have more than one gland localized on preoperative studies or no localization, BNE should be considered. BNE is also indicated in patients with secondary or tertiary hyperparathyroidism in whom parathyroid hyperplasia is most common. In patients with concomitant thyroid disease requiring both parathyroidectomy and thyroidec- tomy, and in cases of parathyroid cancer, the traditional open cervical approach is performed.

BNE is performed through a 3- to 5-cm cervical incision under general anesthesia. The procedure involves identification of usually 4 parathyroid glands, removal of the abnormal glands, and biopsy of one or more normal parathyroid glands. In cases in which more than one parathyroid gland appears abnormal, only the involved glands are excised. IPM can be used as a surgical adjunct to confirm removal of all hypersecreting parathyroid tissue. When not identified initially during BNE, a diligent search for the ectopic abnormal parathyroid gland(s) is performed, involving exploration of the upper mediastinum, retroesophageal area, carotid sheaths, and thyroid gland. If the gland is still not found, the procedure is ended. A planned cervical reexploration, sternotomy, or video-assisted mediastinal parathyroid exploration may be performed at a later date after reevaluation of initial diagnosis and further imaging to localize a possible unidentified mediastinal gland. In conditions of hyperplasia in which all 4 parathyroid glands appear abnormal, subtotal parathyroidectomy (3.5-gland resection) or total parathyroidectomy with autotransplantation is performed. For subtotal parathyroidectomy, the one gland closest to appearing normal is biopsied and subtotally resected first, leaving a tissue remnant of approximately 50 mg. The remaining glands are removed. In cases of total parathyroidectomy, remnant parathyroid tissue is autotransplanted preferably into the brachioradialis muscle of the nondominant forearm with cryopreservation of remaining parathyroid tissue. Bilateral thymectomy is recommended in both surgical approaches due to a high incidence of supernumerary parathyroid glands within this structure.

RADIOGUIDED PARATHYROIDECTOMY

Radioguided parathyroidectomy is another more recent surgical approach used in the treatment of primary hyperparathyroidism. Patients are injected with Tc-99m sestamibi isotope about 2 hours before surgery, and then taken to the operating room where a gamma probe is used to direct the incision site and localize the abnormal parathyroid glands for excision. After the suspected adenoma is removed, the gamma probe is used to measure the radioactivity of the excised tissue, which is compared with the radioactivity of the surgical bed. Radioguided parathyroidectomy may also be useful in reoperative cases, patients who have undergone total thyroidectomy, or cases of ectopic parathyroid tissue. IPM can be used as an adjunct to this technique to increase its operative success rate.

Radioguided parathyroidectomy is usually performed in the ambulatory setting under local anesthesia and sedation. A 2- to 4-cm incision is made at the site of
highest radioactivity that corresponds to the location of the abnormal gland shown by preoperative sestamibi. Investigators report that radioguided parathyroidectomy with the gamma probe achieves 93% sensitivity, 88% positive predictive value, and 83% overall accuracy of parathyroid localization, with a conversion rate to BNE of 10% for single gland disease, 50% for MGD, and 50% for hyperplasia.89,90 Some investigators report that the gamma probe is not helpful in up to 48% of patients who undergo parathyroidectomy due to confusing radioactivity counts, easily identified abnormal glands, equipment problems, and logistical timing problems of isotope administration before surgery.91 The routine use of radioguided parathyroidectomy has not been widely adopted and most parathyroid surgeons do not use this approach, arguing that the gamma probe does not provide additional useful information that can otherwise be obtained with preoperative localization studies and IPM.80–92

ENDOSCOPIC AND VIDEO-ASSISTED PARATHYROIDECTOMY

Recent interest has revolved around the development of minimal access surgical techniques that include endoscopic and video-assisted parathyroidectomy performed with clear preoperative localization, and IPM used to verify the adequacy of abnormal parathyroid gland resection. For the endoscopic approach as described by Gagner, a 5-mm trocar for a 30° laparoscope is first placed at the cervical midline superior to the sternal notch, and carbon dioxide is insufflated to create the work space.93 Another 5-mm port is placed in the right neck about 2 to 3 cm anterior to the sternocleidomastoid muscle. Two additional 5-mm ports are placed for the procedure, one in the right neck and another in the left neck. The strap muscles are divided at midline and the thyroid lobe is mobilized anteromedially to allow for visualization of the ipsilateral parathyroid glands. Many other variations to this technique have been described including axillary, anterior wall, and lateral neck approaches.94–96 Although the technique reportedly has cure rates approaching 100% with excellent cosmetic results, less postoperative pain, fewer analgesic requirements, and increased patient satisfaction, endoscopic parathyroidectomy is associated with the longest learning curve and potential difficulties already described that include parathyroid capsule violation, suboptimal recurrent laryngeal nerve visualization, tachycardia, hypercapnia, respiratory acidosis, subcutaneous emphysema, and air embolism. In contrast, video-assisted parathyroidectomy does not require carbon dioxide insufflation and allows for tactile assessment by the surgeon. Special retractors are used to create the working space. First described by Miccoli, the video-assisted technique is performed using a 5-mm 30° endoscope inserted through a 1.5- to 2-cm transverse incision in the neck.97 The dissection is performed with video magnification that enables easier identification of the recurrent laryngeal nerve and abnormal parathyroid gland. Although this technique has reported cure rates ranging from 96% to 100% with reduced operative time, decreased postoperative pain, and higher patient satisfaction, video-assisted parathyroidectomy requires 2 additional assistants, and may also be associated with a long learning curve.98

Both surgical approaches have not been widely adopted, and most parathyroid surgeons do not consider the techniques more efficacious than the current surgical treatment of primary hyperparathyroidism with focused parathyroidectomy or BNE.99 In addition to the long learning curve necessary to gain proficiency in these techniques, these surgical approaches are contraindicated in patients with large thyroid goiters, previous neck surgery, MGD, MEN or non-MEN familial hyperparathyroidism, equivocal or negative preoperative localization studies, or parathyroid carcinoma. Nevertheless, despite these drawbacks it is the opinion of the chapter authors
that surgeons keen on performing endoscopic or video-assisted parathyroidectomy should have considerable experience with the conventional approaches of focused parathyroidectomy and BNE before attempting these minimal access procedures.

REOPERATIVE PARATHYROIDECTOMY

Reoperative neck exploration for persistent or recurrent disease can be very difficult to perform due to loss of normal tissue planes and replacement by scar tissue. Such operations are associated with higher rates of injury to the recurrent laryngeal nerves as well as permanent hypoparathyroidism. It is therefore paramount that the surgeon review all operative and pathology reports from previous neck operations to determine which parathyroid glands have been removed and remain. Biochemical tests should be repeated to confirm the correct diagnosis of primary hyperparathyroidism. Preoperative laryngoscopy should also be performed for vocal cord assessment before all reexplorations. Furthermore, imaging studies such as sestambi, US, and 4D-CT should be obtained in an attempt to localize the abnormal gland. Parathyroid localization before reoperative parathyroidectomy may minimize unnecessary dissection and reduce potential complications. If such imaging studies fail to localize the abnormal gland, jugular venous sampling in the clinic or selective venous PTH sampling by the radiologist can be performed at medical centers with such experience. At time of reexploration, intraoperative adjuncts such as the radioguided probe or IPM may help localize the abnormal gland and confirm excision and cure. Nerve monitoring may also be useful to the surgeon during reoperative cases.

The most important determinant of success in reoperative parathyroidectomy is an experienced parathyroid surgeon. These procedures, for instance, may require a partial or complete median sternotomy or video-assisted procedure for removal of a mediastinal parathyroid gland. Most of the time, however, the majority of missed parathyroid glands are found in the cervical region. The lateral or “back-door” approach for parathyroidectomy that involves the dissection between the anterior border of the sternocleidomastoid muscle and posterior border of the strap muscles may be implemented. This maneuver is particularly useful in reoperative parathyroidectomy because it provides direct access to the posterior surface of the thyroid gland free of scar tissue from previous operations, performed through the conventional anterior approach. In such initial reoperations, experienced parathyroid surgeons can achieve success rates of up to 94%.

SUMMARY

With the advent of improved preoperative parathyroid localization studies, increased availability of IPM, and the predominance of single-gland disease in most patients with primary hyperparathyroidism, focused parathyroidectomy has become the alternative to conventional BNE. The focused approach has durable cure rates of more than 95%, comparable to BNE, and it can be performed in an ambulatory setting with minimal morbidity. The additional advantages of focused parathyroidectomy include improved cosmetic results with smaller incisions, decreased postoperative pain, shorter operative time, decreased hospitalization, and rapid postoperative recovery, all most beneficial to patients treated for primary hyperparathyroidism. The focused approach has also served as an impetus for further investigation and development of more minimally invasive parathyroidectomy through endoscopic and video-enhanced methods, challenging the current methods of surgical therapy for parathyroid disease. Although some controversy continues to exist as to which operative approach should be considered the standard surgical treatment for primary hyperparathyroidism, nothing
can replace the success of these operations performed by experienced parathyroid surgeons.

REFERENCES

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