Long-Term Success of Surgery for Primary Hyperparathyroidism: Focused Exploration using Intraoperative Parathyroid Hormone Monitoring Versus Four-Gland Exploration

21

Wesley Barnes, Peter F. Czako, and Sapna Nagar

Abstract

Primary hyperparathyroidism is a common problem that is a result of the excessive secretion of parathyroid hormone (PTH) from the parathyroid glands. This is most commonly caused by a single hypersecreting adenomatous gland. Most all patients with primary hyperparathyroidism meet criteria for surgery. The best operation should provide the highest rate of cure with the lowest rate of complications. The standard surgical approach has traditionally been a four-gland exploration. Though this method has endured many years of excellent cure rates, it has been challenged because a long-lasting cure is possible with the removal of a single adenoma in the majority of cases. Thus, a focused exploration via an image-guided, open unilateral exploration employing intraoperative PTH (ioPTH) monitoring has gained popularity over the last two decades. Specifically, ioPTH monitoring has been shown to be paramount to this approach, enabling a more limited exploration by accurately guiding gland excision and predicting postoperative cure. Several large series of focused parathyroid operations have shown excellent, durable cure rates similar to standard four-gland exploration. Focused exploration guided by ioPTH is a safe, effective technique that is recommended for most patients with sporadic primary hyperparathyroidism.

Keywords

Primary hyperparathyroidism · Hypercalcemia · Four-gland exploration · Bilateral neck exploration · Focused parathyroidectomy · Minimally invasive parathyroidectomy(MIP) · Limited parathyroidectomy · Intraoperative parathyroid hormone monitoring (IOPTH)

W. Barnes · P. F. Czako · S. Nagar (✉)
Department of Surgery, Oakland University William Beaumont School of Medicine, Beaumont Hospitals, Royal Oak, MI, USA
e-mail: Sapna.Nagar@beaumont.edu

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Population: Patients with Primary Hyperparathyroidism Undergoing Surgery

Epidemiology

Primary hyperparathyroidism is a common problem with 100,000 new cases detected annually in the United States [1]. It is the third most common endocrine disorder, and the most common cause of hypercalcemia in the nonhospitalized patient [2]. It is more common in women than men. Prevalence depends on the age of the population being studied. It is present in about 1 out of every 500 women and 1 out of every 2000 men over the age of 40 [3]. The typical patient is a postmenopausal female.

For decades after its initial description as a medical disorder, primary hyperparathyroidism was diagnosed after bone or renal complications produced symptoms. However, as routine calcium screening became more common with the advent of automated multichannel analysis in the early 1970s, there was a significant increase in its incidence. As an example, the annual incidence rose from 15 per 100,000 person-years before 1974 (prescreening) to a peak of 112 per 100,000 person-years in 1975 following the introduction of calcium screening in the population of Rochester, Minnesota [4]. This was attributed to the identification of previously unrecognized patients with asymptomatic hypercalcemia and primary hyperparathyroidism [5]. Furthermore, in this Rochester population, the proportion of patients presenting with classical symptoms or complications of primary hyperparathyroidism decreased from 22% in the prescreening era to 6% thereafter [4]. A more recent study from a racially mixed population in Southern California showed that the incidence of primary hyperparathyroidism tripled during the study period from 1995 to 2010, increasing from 76 to 233 per 100,000 female-years and from 30 to 85 per 100,000 male-years [6].

Pathophysiology

Primary hyperparathyroidism is the result of excessive secretion of parathyroid hormone (PTH) from one or more parathyroid glands. Chief cells in the parathyroid gland release PTH mainly in response to low extracellular calcium detected by a calcium-sensing receptor (CaSR) on their cell membranes. Other stimuli of PTH secretion include low levels of 1,25-dihydroxyvitamin D and hypomagnesemia. PTH along with vitamin D and calcitonin regulate serum calcium and phosphorus levels through their interactions with three target organ systems—the skeleton, the kidneys, and the gastrointestinal tract. In the bone, PTH stimulates bone resorption via increased osteoclastic activity. In the kidney, PTH promotes tubular reabsorption of calcium and the hydroxylation of 25-hydroxyvitamin D but inhibits phosphorus absorption. Finally, PTH indirectly stimulates calcium absorption from the gut by increasing 1,25-dihydroxyvitamin D production. As a result of these interactions, PTH serves to increase serum calcium and reduce serum phosphorus. With

rising calcium levels, feedback inhibition of the CaSR on chief cells normally results in a decrease in PTH secretion.

Failure of this feedback regulation permits inappropriately high levels of PTH release. Primary hyperparathyroidism results from the autonomous production of PTH from one of three different pathologic lesions: parathyroid adenoma, parathyroid hyperplasia, or parathyroid carcinoma. Single gland adenomas are the most common cause (accounting for 75–85% of cases); double adenomas are seen in 2–12% of cases, and three gland adenomas represent less than 1–2% of cases. Four-gland hyperplasia is seen in up to 15% of patients with primary hyperparathyroidism, and parathyroid carcinoma is rare—accounting for approximately 1% of cases [2]. In the majority of patients, primary hyperparathyroidism arises spontaneously, and no known cause is identified to explain the loss of calcium sensitivity at the glandular level. Some authors have found an association between exposure of the head and neck to ionizing radiation and the future development of hyperparathyroidism [7]. Although the etiology of sporadic primary hyperparathyroidism is unclear, it is certainly different from secondary or tertiary hyperparathyroidism caused by chronic renal insufficiency and from familial disorders like multiple endocrine neoplasia (MEN) with identifiable genetic abnormalities.

Diagnosis

Clinical Manifestations

In the United States, most patients lack the classic clinical manifestations described by Fuller Albright such as osteitis fibrosa cystica, nephrolithiasis, peptic ulcer disease, pancreatitis, gout and neuromuscular weakness [8]. At first, primary hyperparathyroidism was a disease of the bones, but it soon became evident that kidney stones were more common. Historically, the classic pentad of symptoms included painful bones, kidney stones, abdominal groans, psychic moans, and fatigue overtones. Constipation, anorexia, polyuria, depression, fatigue, and weakness are manifestations of hypercalcemia in general. Only symptoms of fatigue, bone pain, and weight loss seem to correlate with the severity of hypercalcemia [9]. It is estimated that approximately 20% of patients with primary hyperparathyroidism present with symptoms from kidney stones, bone disease, or proximal neuromuscular weakness [10–12]. Nephrolithiasis is the most common complication (15–20%) and less than 5% of patients present with osteitis fibrosa cystica. The clinical presentation often differs drastically in developing countries that do not have access to routine calcium screening. In these situations, the search for classic symptoms unveils the disease [13]. Perhaps these geographical differences in presentation can be explained to some degree by evidence suggesting the disease is more severe in countries where hypovitaminosis D is more widespread [14–16].

Today, the classic skeletal consequence of primary hyperparathyroidism is really only seen in parts of the world where symptomatic disease predominates. Advanced primary hyperparathyroidism is characterized by osteitis fibrosa cystica

(generalized bone pain, fragility fractures, "brown" tumors; radiologic features include salt-and-pepper appearance of the skull, subperiosteal bone resorption of the phalanges, and tapering of the distal third of the clavicle). Although this classic feature is now rare in most places, skeletal involvement remains a critical aspect of the disease. Today, bone mineral density (BMD) testing has become a suitable method for the detection of skeletal complications of asymptomatic primary hyperparathyroidism. BMD measurement is now a standard of care for the evaluation of this disease [17]. Usually, bone loss is most prominent in the distal one-third of the radius (comprised mostly of cortical bone) and least evident at the lumbar spine (comprised mostly of trabecular bone) [18]. Despite data suggesting that the spine is relatively preserved, most studies have demonstrated an increased risk of fractures at all sites—trabecular bone of the spine as well as cortical sites (forearm, hip)—in patients with primary hyperparathyroidism [19–22]. A longitudinal 15-year study out of Columbia revealed progressive BMD losses from cortical sites in 37% of asymptomatic patients over the entire study period [23].

Nephrolithiasis is a key component of the classic pentad of clinical features described previously, and the kidney remains a principal target of primary hyperparathyroidism. The kidney is the organ most likely to demonstrate overt clinical manifestations as a result of the effects of the disease today. Approximately 15% to 20% of patients with primary hyperparathyroidism experience nephrolithiasis. About 3% of patients with stone disease have primary hyperparathyroidism [24]. Kidney stone disease is multifactorial and cannot be explained purely by hypercalciuria. Nevertheless, hypercalciuria is a significant urinary risk factor for the development of calcium oxalate and phosphate stones. Nephrocalcinosis (mineralization of the renal parenchyma) seems to be much less common and not present until disease becomes severe. Primary hyperparathyroidism is associated with renal insufficiency as well; this is demonstrated by a decline in estimated glomerular filtration rate below 60 mL/min in up to 17% of patients suffering from asymptomatic disease [25].

Currently many authors believe that primary hyperparathyroidism is associated with cardiovascular disease, including hypertension, coronary artery disease, heart failure, left ventricular hypertrophy, atherosclerosis, valvular calcifications, and cerebrovascular accidents. Cardiovascular morbidity and mortality were increased in classical primary hyperparathyroidism, but the cardiovascular outcomes from mild or asymptomatic disease continue to be less clear [17]. Studies out of Scotland found increased cardiovascular mortality in primary hyperparathyroidism [26, 27]. Hypertension is frequently associated with this disease, even among those with mild disease [28, 29]. Some studies have found that left ventricular mass [30] and aortic valve calcification area [31, 32] correlate with PTH levels but do not seem to improve following parathyroidectomy. A recent study suggested that the carotid artery may be more affected than the heart, indicating that primary hyperparathyroidism may not initiate but could propagate intimal medial thickness and plaque thickness [32]. However, the degree to which these relationships exist along with the reversibility of such manifestations following surgical correction remains a

topic of considerable debate as most available data are observational. Thus, at this time, there is no evidence to suggest that cardiovascular function or structure should be routinely evaluated in the workup of primary hyperparathyroidism [14].

Today, around 80% of patients diagnosed in the United States are asymptomatic with mild hypercalcemia. Because a biochemical diagnosis is often made incidentally in an asymptomatic patient, the history and physical seldom provide any insight into the diagnosis of primary hyperparathyroidism. However, vague or nonspecific effects on fatigue, cognition, and depression may be more common than previously thought [33].

Initial Investigations

Primary hyperparathyroidism is often initially suspected after an incidental finding of elevated calcium on routine serum chemistry. The total serum calcium should be adjusted for any albumin abnormality. Although ionized calcium can be measured, most centers use total serum calcium concentration. For the hypercalcemic patient, a serum calcium should be repeated in conjunction with intact PTH (iPTH). A diagnosis of primary hyperparathyroidism is established by an elevated PTH concentration in a hypercalcemic patient or by a PTH concentration that is within the mid to upper end of normal range but inappropriately high for a patient's degree of hypercalcemia. The second most common cause of hypercalcemia is malignancy, which can generally be ruled out by an elevated PTH level.

Other laboratory values that are useful in confirming the diagnosis of primary hyperparathyroidism include 24-h urine calcium excretion (elevated in approximately 25% to 35% of patients) and 25-hydroxyvitamin D levels (usually low-normal range) [13]. Patients with primary hyperparathyroidism have a low or low-normal serum phosphorus level and an increased serum chloride-to-phosphorus ratio. Also, these patients exhibit a mild hyperchloremic metabolic acidosis from renal bicarbonate wasting. Differential diagnosis of the hypercalcemic patient with an elevated PTH also includes familial hypocalciuric hypercalcemia (FHH), hyperparathyroidism secondary to lithium or thiazide diuretic administration, and tertiary hyperparathyroidism seen with end-stage renal disease.

Formally recognized in 2008, normocalcemic hyperparathyroidism has been detected most often through the evaluation of individuals with osteoporosis and recurrent nephrolithiasis [34, 35]. The diagnosis of normocalcemic hyperparathyroidism is a challenge. In order to make a diagnosis, all secondary causes of hyperparathyroidism must be ruled out, ionized calcium levels should be normal, and the serum 25-hydroxyvitamin D level should not be below the lower limit of normal. It is not yet clear whether patients with this normocalcemic variant in fact have an early form of primary hyperparathyroidism, and thus their calcium levels, if followed long enough, would be expected to rise [36, 37]. However, this variant remains incompletely described with regard to its epidemiology, natural history, and management [17].

Natural History of Asymptomatic Primary Hyperparathyroidism Without Surgery

As mentioned previously, prior to the introduction of automated equipment for analyzing routine serum calcium levels, primary hyperparathyroidism was a symptomatic disorder in which debilitating bone disease, kidney stones, and muscular weakness were common. Throughout history, symptomatic patients have continued to undergo parathyroidectomy for prevention of disease progression and relief of symptoms. However, the majority of patients today seem to have a milder form of the disease and, thus, treatment decisions that are rooted in risk-benefit analyses hinge largely on the natural history of the disease. A prospective 10-year follow-up study was begun at the Mayo Clinic in 1968, and it showed that the majority of asymptomatic patients who were followed without surgery did well with no significant disease progression [38]. Later, Rao et al. examined the course of 80 untreated asymptomatic patients for up to 11 years; there were no episodes of worsening hypercalcemia, renal function, nephrolithiasis, or densitometric indices during this period [39]. These studies and others like them validated the nonoperative surveillance of mild asymptomatic primary hyperparathyroidism by reporting that rapid progression of biochemistry, symptoms, or metabolic complications is uncommon with borderline hypercalcemia.

However, a longitudinal 15-year follow-up study out of Columbia University Medical Center published in 2008 demonstrated that BMD in cortical sites (distal radius, femoral neck) declines over time in asymptomatic patients who do not undergo surgery regardless of administration of antiresorptive therapy, but BMD improves following parathyroidectomy [23]. Furthermore, 37% of asymptomatic patients in this study showed disease progression (i.e., developing one or more new indication for surgery during the study period) [23]. In another study, patients younger than 50 years of age were about three times more likely to have disease progression [40]. Several studies have provided more data on the natural history of untreated asymptomatic primary hyperparathyroidism [41–43]. Biochemistries may remain largely unchanged for up to 12 years, and BMD is stable for up to 8 years [23]. However, long-term observation seems suboptimal for skeletal outcomes. These data led to the consensus response that surgery is appropriate in the majority of patients with asymptomatic primary hyperparathyroidism despite evidence for biochemical and densitometric stability with nonsurgical surveillance because current data suggests that this stability is not indefinite [44].

Surgical Management of Primary Hyperparathyroidism

The approach to managing patients with primary hyperparathyroidism has undergone several changes over the last few decades. Yet, parathyroidectomy remains the only definitive cure [45]. There is universal agreement that all symptomatic patients should undergo surgery. However, the optimal treatment strategy for asymptomatic patients is less clear. In order to provide an evidence-based consensus on the

management of asymptomatic primary hyperparathyroidism, the National Institutes of Health (NIH) met in 1990, 2002, and 2013 to develop guidelines for the surgical treatment of this disease (Table 21.1). Surgery is also indicated in patients who refuse to undergo medical surveillance and in patients opting for an operation even if they do not meet any guidelines [14]. Following successful parathyroidectomy, kidney stone formation is reduced in those with a history of stones, bone density improves, fracture incidence decreases, and subjective improvements in

Table 21.1 PICO table

P	Population	Patients with primary hyperparathyroidism undergoing surgery: • Symptomatic primary hyperparathyroidism • Asymptomatic primary hyperparathyroidism with following indications [14]: – Age <50 years – Serum calcium 1.0 mg/dL above the upper limit of normal – BMD by DXA: T-score <−2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 of radius – Vertebral fracture by radiograph, CT, MRI, or VFA – Creatinine clearance <60 mL/min – 24-h urinary calcium >400 mg/day and increased calcium-containing stone risk by biochemical analysis – Presence of nephrolithiasis or nephrocalcinosis by radiograph, ultrasound, or CT
I	Intervention	Four-gland exploration has served as the gold standard for several decades, demonstrating cure rates that range from 95 to 99% and a low risk of permanent recurrent laryngeal nerve injury (<1%) and permanent hypoparathyroidism (<0.5%)
C	Comparator	Focused exploration via an image-guided, open unilateral exploration employing ioPTH. With ioPTH monitoring, the surgeon can: • Make an objective determination of cure in the operating room • Often perform a more limited procedure with a potential to decrease risk of injuring the recurrent laryngeal nerves and other normal parathyroid glands
O	Outcome	A review of the literature comparing focused exploration using ioPTH monitoring to traditional four-gland exploration demonstrates the following: • No statistically significant difference in persistent primary hyperparathyroidism, which ranged from 0% to 4% for focused exploration • No statistically significant difference in recurrent primary hyperparathyroidism, which ranged from 0% to 4% for focused exploration • No statistically significant difference in complications (recurrent laryngeal nerve injury, permanent hypoparathyroidism, cervical hematoma, wound infection, etc.) Focused exploration guided by ioPTH is a safe, effective technique that is recommended for most patients with sporadic primary hyperparathyroidism (moderate quality GRADE recommendation)

BMD bone mineral density, *CT* computed tomography, *DXA* dual-energy X-ray absorptiometry, *MRI* magnetic resonance imaging, *VFA* vertebral fracture assessment, *ioPTH* intraoperative parathyroid hormone

neurocognitive elements as well as quality of life are noted [14]. Cardiovascular disease is one of the most common causes of mortality in patients with both treated and untreated primary hyperparathyroidism [46–51]. However, at this time, parathyroidectomy should not be performed for improvement of cardiovascular endpoints [14]. Even with these guidelines in place, there still remains no true agreement among practicing endocrinologists and endocrine surgeons about whether most patients should be referred for parathyroidectomy or surveyed while administering medical therapy. Furthermore, the majority of patients who meet surgical criteria are not undergoing surgery [52].

Intervention: Four-Gland Exploration

When surgery is indicated, the surgeon must choose the appropriate operative approach. The best operation among these choices should give the highest rate of cure with the lowest rate of complications. Traditionally, since Felix Mandel's report of the first successful parathyroidectomy in 1925, the surgical management of primary hyperparathyroidism involved a bilateral neck exploration with visualization of all four glands and removal of one or more enlarged glands [53]. However, minimally invasive parathyroidectomy (MIP) has gained popularity with improvements in preoperative localization techniques and the development of intraoperative parathyroid hormone (ioPTH) monitoring. The definition of "minimally invasive" encompasses procedures that use open, endoscopic, and robotic-assisted techniques. This chapter will focus on comparing a bilateral exploration with an image-guided, open unilateral exploration employing ioPTH, which will be referred to as a "focused exploration."

Technique of Four-Gland Exploration

This procedure relies on an expert understanding of parathyroid embryology as well as normal and variant anatomy of the glands. Upon establishing a diagnosis of primary hyperparathyroidism, preoperative workup should include risk stratification of undergoing anesthesia and possible endoscopic evaluation of the vocal cords.

At our institution, the patient is placed under general anesthesia and positioned with a roll beneath the shoulders and the neck extended. The neck is open via a symmetrical transverse collar incision overlying the thyroid isthmus, which is typically about two fingerbreadths above the suprasternal notch. The platysma is divided, and a skin-platysma flap is developed within a relatively avascular plane just deep this muscle. The cervical fascia is divided in the midline and strap muscles separated from the underlying thyroid as well as thymus. Next, the thyroid lobe on the side to be explored is rotated anteriorly and medially. Sometimes the ipsilateral middle thyroid vein must be divided to allow this maneuver. In order to facilitate identification of the parathyroid glands, the surgical field should remain bloodless if possible because blood staining of the tissues can make exploration quite difficult.

The right upper parathyroid gland is sought first, followed by identification of the right lower gland. With the thyroid rotated anteromedially, the surgeon examines the tissues posterior to the lobe. A thorough understanding of the relationships seen with both normal and aberrant parathyroid anatomy is critical. A delicate dissection is carried out in the usual locations first. However, when a gland is unable to be identified in its normal location, the search is continued for an ectopic gland. Any abnormalities should be investigated. Normal parathyroid glands are a light yellow-brown color, whereas adenomatous glands take on a reddish-brown color. Suspicious fat lobules should be inspected and opened because the inferior parathyroid glands are often surrounded by thymic fat. The recurrent laryngeal nerve is not exposed routinely, but the surgeon must be familiar with its course so as to protect it from harm at all times. After both right-sided glands have been identified, the contralateral neck should then be explored in a similar manner. In general, all four glands should be discovered before any gland is removed. When a solitary adenoma is found, the vascular pedicle of the gland is ligated and then resected. If more than one parathyroid gland is enlarged, they are resected, and normal glands are marked with a metallic clip to facilitate identification should re-operation be necessary. At least one of these normal-appearing glands should be biopsied and sent as frozen section to rule out parathyroid hyperplasia. A subtotal parathyroidectomy is performed when all four glands are abnormal.

Outcomes Following Four-Gland Exploration

The goal of parathyroid surgery is the excision of all hyperfunctioning glands so as to cure the patient's disease, achieve normocalcemia, reverse metabolic complications, and relieve symptoms. The results for bilateral cervical exploration are outstanding.

Cure Rates

Bilateral parathyroid exploration has served as the standard operation for a successful cure of hyperparathyroidism for 90 years. The ultimate goal of parathyroidectomy for primary hyperparathyroidism is to achieve postoperative eucalcemia that is both immediate and long-lasting. Although persistent and recurrent primary hyperparathyroidism are often presented as combined surgical outcomes, they are two very different entities. If elevated serum calcium is seen within the first 6 months postoperatively, then that patient is said to have persistent hyperparathyroidism. A failed initial operation is most often the result of surgeon inexperience, missed parathyroid adenoma (either in a normal or ectopic location), undiagnosed second adenoma, or misdiagnosis of parathyroid hyperplasia [54–57]. On the other hand, if hypercalcemia returns after 6 months of normocalcemia postoperatively, this is considered recurrent hyperparathyroidism. Whether this results from metachronous postoperative autonomous hypersecretion of a previously normally functioning

gland or from a synchronous additional latent abnormal gland that was previously unrecognized is a matter of debate. Multiple studies have demonstrated high surgical cure rates, ranging from 95% to 99%, with bilateral neck exploration and excision of all macroscopically enlarged parathyroid glands or histologically abnormal glands [58–65]. Recurrence following the traditional approach ranges from 0.4% to 5% [58, 60, 62, 66–70]. The importance of an experienced surgeon cannot be overstated. In a 1988 study out of Scandinavia, it is clearly demonstrated that up to 70% of patients may fail to become normocalcemic in the hands of less experienced surgeons performing fewer than ten operations for primary hyperparathyroidism annually [71].

Complications

Major complications following bilateral neck exploration and parathyroidectomy are rare. The overall combined perioperative morbidity is less than 4% in most reported series [45]. This rate may be slightly higher in the elderly patient undergoing general anesthesia. Mortality is rare if not nonexistent in the majority of studies.

Hoarseness is a postoperative finding that is often indicative of a recurrent laryngeal nerve injury, which may be transient or permanent. Injury may be a result of crushing or traction as opposed to actual transection of the nerve [72]. However, this hoarseness may be the result of endotracheal intubation, which can have an incidence up to 40% [73]. Permanent recurrent nerve injuries are generally reported to be less than 1% at the time of initial exploration [62–65]. Injuries involving the external branch of the superior laryngeal nerve are often subtle clinically and less likely to be reported [45]. Meticulous dissection by a surgeon well versed in the possible variations of the course of these nerves helps to avoid injury.

Postoperative hypocalcemia to some degree occurs relatively frequently, especially in patients who are severely hypercalcemic or chronically vitamin D deficient preoperatively. This is usually transient in nature and managed on an outpatient basis with oral calcium and vitamin D supplementation. Symptoms of hypocalcemia include perioral or digital paresthesias, anxiety, tetany, and seizures. Mild hypocalcemia is often caused by a transient relative hypoparathyroidism, resulting from a delay of normal parathyroid glands in returning to their baseline functional status after a period of suppression by hyperactive tissue. Permanent hypoparathyroidism is much less common but can occur secondary to ischemia from a failure to preserve the blood supply to normal parathyroid glands or following subtotal parathyroidectomy for multigland disease with nonviable remnant tissue. In a study of 1112 patients undergoing bilateral neck explorations for primary hyperparathyroidism, transient hypocalcemia was seen in 1.8% of patients with no patients suffering permanent hypoparathyroidism [63]. Other studies demonstrate similar results with permanent hypocalcemia rates less than 0.5% [60, 65].

Wound infections and neck hematomas are rare (<1%), but a potentially fatal airway obstruction can occur from a rapidly expanding hematoma that should be

managed emergently with evacuation if encountered. Despite the observed success and limited morbidity of this approach, there has been a steady worldwide trend toward a more focused, unilateral exploration.

Comparator: Focused Exploration Using Intraoperative Parathyroid Hormone Monitoring

Historical Perspective of Unilateral Exploration

The operative approach to parathyroid exploration has undergone a major shift over the past three decades. Although the bilateral neck exploration has endured many years of excellent cure rates, it has been challenged because a long-lasting cure is quite often possible with the removal of a single adenoma—accounting for up to 85% of cases of sporadic primary hyperparathyroidism.

Unilateral neck exploration was initially advocated by Wang [74] and later by Tibblin [75] in the 1970s when an adenoma and a normal gland were found on the same side. The Lund University surgeons advocated for intraoperative oil red O staining of frozen sections of the macroscopically normal ipsilateral gland to exclude the possibility of multiglandular disease [75]. In principle, the goal was to restrict the neck exploration to the side with the solitary adenoma. At first, surgeons did not use localization studies, and so approximately half of patients had the correct side explored originally. If the wrong side was explored initially, an adenoma was sought on the opposite side. Then, there was a surge of interest in parathyroid localization with preoperative imaging. Early efforts often were of limited value leading to the often quoted remark by Doppman, an interventional radiologist, who said the "only localizing study necessary for primary hyperparathyroidism is to locate an experienced parathyroid surgeon." [76, 77] However, over the following decades, we have seen a trend toward a focused exploration. This paradigm shift is primarily attributable to the advancements made in the accuracy of preoperative localization tests and availability of ioPTH monitoring.

Preoperative Localization Tests

In an effort to improve the surgeon's likelihood of initially exploring the correct side beyond that of mere random chance, preoperative imaging studies have been developed to guide the surgeon to the side with the adenoma. The strategy involves knowledge of and dissection on the side of the adenoma, thus reducing the operating time, cost, and possibly some of the morbidity associated with the procedure. No localization study should be regarded as diagnostic. These tests are meant for operative planning, and so it follows that they are unnecessary if a patient is not an operative candidate [78]. Thus, the surgeon in collaboration with the radiologist or nuclear medicine physician should be making the decisions regarding parathyroid localization [45]. Preoperative imaging is not required for bilateral neck exploration in the

"virgin neck" because all four glands will be investigated intraoperatively. Consequently, localization is most appropriate when a focused approach or a reoperative neck case is planned.

Multiple imaging modalities are available for identifying the offending parathyroid gland(s). They can be divided into invasive and noninvasive tests. Noninvasive imaging studies include ultrasonography, technetium 99m (^{99m}Tc)-sestamibi scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI). Invasive options consist mainly of selective venous sampling and parathyroid arteriography.

Ultrasound

Cervical ultrasonography for the evaluation of parathyroid glands was first described in the late 1970s [79, 80]. Preoperative parathyroid ultrasonography was introduced at our institution a few years later, and we reported on our initial experiences with this technique between 1979 and 1988 [81]. Normal glands are uncommonly visualized with this modality. Retroesophageal lesions are infrequently visible, and ultrasound cannot be used to locate mediastinal glands because it cannot penetrate the sternum. Parathyroid adenomas are characteristically homogeneous, hypoechoic structures with a peripheral rim of vascularity on ultrasonography employing gray-scale and color Doppler imaging [82]. A meta-analysis that included 19 studies reporting results on parathyroid ultrasound demonstrated a pooled sensitivity and positive predictive value (PPV) of 76% and 93%, respectively [83]. This study included only patients at the time of initial presentation with primary hyperparathyroidism regardless of etiology, but another review of the literature [84] showed that sensitivity diminishes for patients with double adenomas (16%) and multiglandular hyperplasia (35%). Smaller gland size, ectopic gland location under the sternum or behind clavicles, and patient obesity have also been shown to limit the detection of abnormal glands [85].

Ultrasound is attractive because it is widely available, it is inexpensive, it does not expose the patient to ionizing radiation, and it can be performed by the surgeon. Also, concomitant thyroid pathology is seen in approximately 20% to 30% of patients with primary hyperparathyroidism [86]. Cervical ultrasound is a sensitive technique for evaluating the thyroid for synchronous nodules and preparing for the possibility of simultaneous parathyroid-thyroid surgery [87–89]. Although ultrasound has been successful in the localization of larger adenomas found within the neck in the absence of concurrent thyroid pathology, the accuracy of this modality is highly dependent on skilled sonographers performing and interpreting the study [81, 90–93].

Sestamibi Scintigraphy

Young et al. initially described the ability to reliably locate parathyroid adenomas utilizing thallium-201 (^{201}Tl) and ^{99m}Tc subtraction scintigraphy in 1983 [94]. In 1989, Coakley et al. reported that ^{99m}Tc-sestamibi, which was being used for cardiac imaging at the time, also was concentrating within parathyroid tissue [95]. A variety of nuclear scintigraphic agents have been employed, but ^{99m}Tc remains the agent of choice today. Mitochondrial uptake of ^{99m}Tc-sestamibi occurs in both the thyroid

and parathyroid glands, but the radioisotope is retained longer by the mitochondria-rich parathyroid glands. Normal parathyroid glands are not seen on sestamibi scintigraphy, but hyperfunctioning tissue more avidly concentrates ^{99m}Tc-sestamibi. A review of the literature demonstrates a wide range of sensitivities for sestamibi scanning. One meta-analysis of 52 studies reported sensitivities from 39% to greater than 90% [96]. Parathyroid hyperplasia and multiple adenomas can cause false negative results [97], and concurrent thyroid disease, particularly follicular and Hurthle cell thyroid neoplasms, may result in false positive results [98, 99]. Another meta-analysis found an overall sensitivity of 88% for single adenomas, 30% for double adenomas, and 44% for multiple gland hyperplasia [84].

Similar to ultrasonography, the advantages of ^{99m}Tc-sestamibi include widespread availability and relatively low cost. Sestamibi scanning is less operator dependent than ultrasound, and its wider field of view facilitates the evaluation of ectopic glands, namely those in the mediastinum or retroesophageal locations [95]. Also, like ultrasound, sestamibi scintigraphy is more accurate in predicting the side rather than the quadrant of a single adenoma [100]. Scintigraphy does result in a modest dose of radiation.

Sestamibi scanning can be enhanced by three-dimensional imaging through its fusion with single-photon emission computed tomography (^{99m}Tc-SPECT or SPECT) and with CT (^{99m}Tc-SPECT/CT or SPECT/CT) to yield more readily interpretable images as well as provide better anatomic detail. The additional dimension improves detection of ectopic glands and multiglandular disease along with overall sensitivity compared to planar imaging. A meta-analysis of 9 SPECT studies reports a pooled sensitivity and PPV of 79% and 91%, respectively, for this modality [83]. Another meta-analysis reviewing 24 studies showed a pooled sensitivity of 86% for SPECT/CT, which was superior to the sensitivities of SPECT (74%) and planar (70%) techniques [101]. Although these results are encouraging, SPECT/CT results in both increased cost and radiation exposure [78]. Also, by adding delayed sestamibi scans (so called dual-phase imaging) or subtraction techniques to planar, SPECT, or SPECT/CT, even higher accuracy may be obtained by decreasing false positives that result from concurrent thyroid lesions or lymph nodes [102]. However, multiglandular disease remains difficult to image whether employing SPECT or SPECT/CT. Based on this data, dual-phase SPECT or SPECT/CT is often the preferred imaging modality for parathyroid localization prior to initial exploration by most surgeons.

Computed Tomography

Although standard CT with intravenous contrast has been used in the evaluation of parathyroid adenomas, its sensitivity has been inferior to that of other techniques, and it exposes the patient to more radiation than other modalities. Yet CT can be helpful in visualizing mediastinal tumors as well as those in a retroesophageal location. Four-dimensional CT (4D-CT) is an imaging modality that relies upon the characteristic rapid uptake and washout of contrast from parathyroid adenomas. The fourth dimension is time. 4D-CT seems particularly useful in reoperative neck cases where other initial imaging studies (sestamibi and ultrasound) fail to localize a tumor. In a study of 45 patients with primary hyperparathyroidism who had

undergone previous neck exploration, 4D-CT demonstrated 88% sensitivity for abnormal parathyroid glands compared to SPECT or neck US (54% and 21%, respectively) [103]. 4D-CT also seems highly effective in detecting the presence of multiglandular disease and the location of ectopic glands [104]. Compared to SPECT, 4D-CT results in a modest increase in total radiation dose; however, the radiation dose to the thyroid with 4D-CT is 57 times that of SPECT [105]. This must be considered particularly in young patients, who tend to have a higher risk of thyroid cancer [105]. In addition to the radiation exposure, 4D-CT is not widely available, and it is difficult to interpret.

Invasive Localization

Venous catheterization with sampling for PTH, referred to as selective venous sampling (SVS), as well as parathyroid arteriography have largely been replaced by the above described noninvasive imaging modalities. However, these more invasive options still may play a role in lateralizing the side of disease in difficult reoperative cases with inconclusive, contradictory, or nondiagnostic noninvasive localization studies [78].

In summary, ultrasound, sestamibi scintigraphy, and CT scans are the most commonly utilized localization studies today [90]. The most preferred approach to localizing abnormal parathyroid glands in a patient with an initial diagnosis of primary hyperparathyroidism is combining ^{99m}Tc-SPECT with cervical ultrasound. Four-dimensional CT is reserved for equivocal or discordant initial imaging results. Preoperative localization is most commonly utilized today when a focused exploration is planned or in patients with prior history of a neck operation. With experienced sonographers and nuclear medicine physicians, the combination of SPECT and ultrasonography can accurately localize greater than 90% of single parathyroid adenomas preoperatively [106]. However, as discussed above, these localization studies may fail to recognize double adenomas and multiple gland hyperplasia. Moreover, nonlocalizing studies seem to be more common in patients with multiglandular disease [107]. Traditionally in cases of multigland disease, one-third of patients will have a negative scan, one-third will have a scan consistent with a single adenoma, and one-third will have a scan showing more than one abnormal gland [108, 109]. It should be emphasized that negative or discordant imaging studies should not discourage physicians from referring a patient to an endocrine surgeon [78]. Because the incidence of multiglandular disease is reported between 4% and 30% [110–119], reliance on imaging alone appears to increase the operative failure rate [107, 120, 121]. Thus, other adjuncts have been applied to rule out multiglandular disease intraoperatively.

Intraoperative Localization Tests

Intraoperative Gamma Probe

Some surgeons have promoted utilization of an intraoperative gamma probe as a useful aid in parathyroid exploration [122, 123]. Following the intravenous administration of ^{99m}Tc-sestamibi preoperatively, hyperfunctioning parathyroid glands are identified by a handheld gamma probe that assesses sestamibi uptake. However, the

expert panel constituted by the Committee of the Fourth International Workshop on the Surgical Management of Asymptomatic Primary Hyperparathyroidism does not advocate routine use of this technique [45]. It is an adjunct that may be employed in reoperative cases.

Intraoperative Parathyroid Hormone Monitoring

A focused parathyroidectomy utilizes preoperative localization (where to start) and intraoperative PTH monitoring (when to stop) to guide operative success as well as to minimize dissection and time in the operating theater. Theoretically, once all hyperfunctioning tissue has been resected, the circulating levels of PTH should decline. If levels fail to decline, then additional hyperfunctioning tissue needs to be removed. Because of the short half-life of PTH (mean half-life of 3.5 to 4 min), it is ideal for monitoring intraoperatively in order to prove that surgical cure has been accomplished. Nussbaum and coworkers first described intraoperative measurement of intact PTH in 1988 using a two-site antibody technique that proved more sensitive and specific than previous assays [124]. In 1991, Irvin et al. modified Nussbaum's technique and reported on a quick method for intraoperative PTH (ioPTH) monitoring as a "biochemical frozen section" that would provide feedback within 15 min [125]. A rapid PTH assay then became commercially available in 1996, facilitating its widespread utilization in the operating room. Since this time, ioPTH has been employed more and more frequently during parathyroid surgery, particularly with focused exploration.

There are numerous assays available for intraoperative use today, but the principles underlying their use in the operating room are similar for all. The ioPTH assay confirms the resection of all hyperfunctioning parathyroid glands, helps to direct decisions regarding need for further cervical exploration, and allows for a focused unilateral parathyroid exploration. Furthermore, PTH levels can be analyzed from fine-needle aspirates or frozen sections to determine if suspicious tissue is indeed a parathyroid gland in the operating room rather than a lymph node or thyroid nodule [126]. Lastly, the assay can also be used to lateralize the side of the neck that is harboring hypersecreting tissue through the measurement of a jugular venous gradient in patients with equivocal preoperative imaging studies.

A considerable amount of controversy surrounds the criterion that should be used to predict operative success, as the accuracy of this surgical adjunct seems to depend on the timing and frequency of ioPTH measurements as well as the percentage drop in PTH levels from baseline values. An optimal algorithm for ioPTH monitoring is one that accurately validates cure—particularly for multiglandular disease—as well as minimizes unnecessary cervical exploration, resection of normally functioning parathyroid glands, operative time, and number of blood draws. In 1993, Irvin first described the "Miami criterion" that could be used to predict a postoperative return to normocalcemia [127]. This criterion is defined as a 50% or more drop in ioPTH from the highest of either the pre-incision or pre-excision level at 10 min after resection of all hyperfunctioning tissue [110, 127]. Since this criterion was established, a significant amount of work has gone into defining the optimal interpretation strategy of ioPTH values. Several other authors have developed protocols for monitoring changes in ioPTH dynamics in

an attempt to better confirm operative cure (Table 21.2). Furthermore, scoring models that utilize either pre- or intra- operative variables are available to predict the likelihood of multiglandular disease and thus those most likely to benefit from further neck exploration [128, 129].

In the operating room, peripheral vein cannulation is most commonly used for collection of blood samples. Jugular venous sampling often demonstrates higher overall absolute ioPTH values when compared to peripheral samples, thus increasing the time it takes ioPTH levels to decline adequately and possibly leading to unnecessary neck explorations. Vein access is kept open with saline infusion throughout the procedure. Only 2–3 mL of whole blood is needed for ioPTH measurement, but prior to taking this sample 10 mL of blood is discarded to avoid sample dilution by saline infusion. The blood sample is placed in an ethylenediaminetetra-acetic acid (EDTA) coated glass tube. Routinely performing blood draws at specific intervals during parathyroidectomy allows for reliable analysis of intraoperative hormone dynamics. When following the Miami criterion, samples are most commonly taken at the following times: (1) before skin incision is made (pre-incision); (2) just before dividing the blood supply to the suspicious parathyroid gland (pre-excision); (3) at 5 min after excision of the suspected gland; and (4) at 10 min post-excision. During the 8 to 15 min of turnaround time for ioPTH assays, the surgeon can close the incision. Manipulation of the remaining normal parathyroid glands can falsely elevate PTH levels and delay hormone decline, thus manipulation should be avoided when closing. If the assumed criterion is not met with the 10-min level, then the surgeon should pursue further neck exploration by finding the other ipsilateral gland before moving to the contralateral side and employ the same protocol for each additional hyperfunctioning gland removed.

Table 21.2 Criteria for intraoperative parathyroid hormone (ioPTH) decline to predict cure

Miami criterion [110]	An ioPTH drop by 50% or more from the highest of either pre-incision or pre-excision level at 10 min post-excision
Vienna criterion [113]	An ioPTH drop by 50% or more from the baseline (pre-incision) within 10 min post-excision
Halle criterion [113]	An ioPTH drop into the low-normal range (≤35 pg/mL) within 15 min post-excision
Rome criterion [134]	An ioPTH drop by greater than 50% from the highest pre-excision level, and/or ioPTH concentration within the reference range at 20 min post-excision, and/or ioPTH less than or equal to 7.5 pg/mL lower than the value at 10 min post-excision
Wisconsin rule [132]	An ioPTH drop by 50% or more from the baseline (pre-incision) at 5, 10, or 15 min post-excision • If the 5-min post-excision value is elevated above the baseline pre-incision value, then the "baseline" should be reset to this peak (5-min) value, and curative resection is then predicted by a 50% fall in the ioPTH level from the redefined 5-min ioPTH peak within 15 min of this peak (approximately 20 min after resection of the initial gland)
Mayo protocol [140]	An ioPTH drop by 50% or more from baseline (pre-excision) to a normal (or near normal) level at 10 min post-excision

The PTH level measured for diagnosis of primary hyperparathyroidism should not be used as the pre-incision sample. All values should be collected under the same conditions and using the same assay that will be utilized in the operating room. The second or pre-excision sample will help to capture any decrease or increase in circulating PTH that may have occurred during gland dissection. Refer to Table 21.3 regarding definitions used to calculate the accuracy of ioPTH. Carniero et al. proposed that inadvertent premature devascularization of the hyperfunctioning gland during dissection may result in a pre-excision value that has already fallen below the pre-incision value [110]. Riss et al. reported that PTH spikes, defined as an increase in PTH exceeding 50 pg/mL before excision of the gland, resulting from the manipulation of hypersecreting glands may occur in 15% to 50% of patients [130]. For example, the Miami criterion could incorrectly predict a cure (i.e., false positive) before removal of any tissue if the highest ioPTH value was to be obtained during one of these spikes. Also, one can debate whether this elevated ioPTH level is a true reflection of the patient's PTH level, and so it follows that a 50% drop from this falsely elevated level might result in increased failure rates. Chiu and colleagues reported that always using the pre-incision level as baseline may actually detect more abnormal glands by reducing false positives [131]. On the other hand, spikes occurring at the time of adenoma removal might result in a delayed decay of ioPTH and incorrectly predict the presence of additional hyperfunctioning tissue (i.e., false negative), thus leading to unnecessary bilateral explorations [130]. To cut costs incurred by multiple measurements, some surgeons employ a protocol that does not include a pre-excision value. However, when a pre-excision level is not obtained, a 50% drop may not be obtained at 10 min post-excision because of the aforementioned PTH spike that may occur. A criticism of this method is that it results in too many unnecessary continued neck explorations [110]. Because this PTH stimulation may be the result of surgical manipulation as opposed to multigland disease, a few studies [45, 130, 132] recommend that the surgeon should attempt to wait for the ioPTH to fall below 50% of the pre-incision baseline value, especially if the suspicious gland was correctly located by preoperative imaging. The Wisconsin rule was developed to help obviate this potential pitfall and avoid any unnecessary exploration [132]. Barczynski et al. showed that using the Miami criterion without adding 15 and 20 min post-excision samples may contribute to a higher number of false negative explorations [115]. In addition, prolonged PTH clearance in patients with subclinical renal insufficiency may contribute to false negatives [130].

Table 21.3 Definitions used to calculate the accuracy of intraoperative parathyroid hormone (ioPTH) with the Miami criterion in predicting postoperative calcium levels

	Operative success (normal or low calcium for ≥6 months postoperatively)	Operative failure (high calcium within 6 months postoperatively)
ioPTH drop by ≥50%	True positive	False positive
ioPTH drop by <50%	False negative	True positive

The Miami criterion is the most commonly employed algorithm today [45]. In 2004, Irvin et al. reported that this criterion predicted postoperative calcium levels with a false negative rate of 2%, a false positive rate of 1%, a sensitivity of 98%, a specificity of 96%, and an overall accuracy of 98% [133]. However, there have been variable success rates reported in the literature utilizing this algorithm to predict cure, largely attributed to missed double adenomas or multiglandular hyperplasia [109, 114, 134–137]. For example, Siperstein et al. published a large study to evaluate the prevalence of additional parathyroid pathology following focused parathyroidectomy by continuing with bilateral exploration with excision of additional enlarged glands despite a significant drop of ioPTH levels [114]. In this study, the authors suggest that unrecognized enlarged glands may be left in situ in at least 16% of patients, risking future recurrent hyperparathyroidism [114]. However, the Miami group claims that ioPTH monitoring does not miss multiglandular disease in a review of its 10-year outcomes with a mean follow-up of 83 months where the recurrence rate was 3% [138]. In fact, the main cause of operative failures in another study by the Miami group was the surgeon's inability to find the abnormal gland rather than missed multiglandular disease [139]. Other investigators have suggested stricter criteria or alternative interpretations so as to reduce the reported incidence of false positives (i.e., failure to recognize multigland disease and achieve cure despite a sufficient drop in hormone levels) [113, 134, 135, 140]. Richards and colleagues reported on the Mayo protocol, stating that it had the highest sensitivity (96%), PPV (99%), and accuracy (95%) compared with other strategies, including a 50% drop from baseline at 10 min post-excision [140]. Specifically, with respect to multiglandular disease, the Mayo protocol [141] may have a higher sensitivity (95%), specificity (100%), and accuracy (97%) compared to that reported by the Miami group—90%, 94%, and 92%, respectively [110]. Another study suggests that even stricter criteria (post-excision ioPTH level that is ≥75% lower than baseline and within normal range) should be used to predict success when multiglandular disease is recognized [142]. However, stricter criteria than the Miami criterion were estimated to increase operative success by only 0.3% but significantly increase unnecessary bilateral explorations to 20% in one study [143]. In general, attempts at improving detection of multiglandular disease by lowering the number of false positive outcomes have resulted in an increased specificity but at the cost of further unnecessary neck explorations with prolongation of operative time through an increase in false negatives, lower sensitivity and lower overall accuracy [115].

Because the various criteria for ioPTH monitoring were not found to be equivalent in predicting cure or detecting multiglandular disease, there have been multiple studies comparing these strategies [110, 113, 115, 131]. Barczynski et al. performed a retrospective review of the Miami, Vienna, Halle, and Rome ioPTH criteria [115]. This study found that the Miami criterion followed by the Vienna criterion had the highest overall accuracy in predicting cure (97% and 92%, respectively) while the Rome criterion followed by the Halle criterion was most useful in the intraoperative detection of multiglandular disease. In contrast, another study by Riss et al. found

that the Vienna and Halle criteria correctly detected multiglandular disease in 91% of patients, whereas the Miami criterion did so in only 57% of patients [113]. A criticism of some of these comparison studies is that the incidence of multiglandular disease ranged from only 4% to 7% [110, 113, 115, 117–119, 144, 145], whereas a rate of 15% to 30% is reported by other groups [111, 112, 114]. It is possible that these higher rates may overestimate the true incidence of multiglandular disease as these unrecognized enlarged glands are not necessarily hyperfunctioning, thus may not be contributing to hyperparathyroidism. Long-term follow-up data is needed to determine whether these are in fact "latent" adenomas increasing the chance for recurrence or just enlarged "nonsecreting" glands. Variations in multiglandular disease may also be associated with regional differences in vitamin D deficiency, familial disease, and referral patterns [140].

Another point of contention regards the role of ioPTH for the patient with concordant imaging studies. In up to two-thirds of cases, both sestamibi and ultrasound imaging identify the same, solitary adenoma in patients with sporadic primary hyperparathyroidism. In this setting, a focused exploration without ioPTH monitoring has been shown to be successful in 96% of patients [108], and so some authors will not perform ioPTH monitoring for these patients with concordant imaging studies because they feel it would be of little value [146, 147]. However, as discussed above, all hyperfunctioning glands cannot be accurately localized preoperatively in the majority of patients with multiglandular disease. Thus, ioPTH monitoring can help to solve this issue and improve operative success [107, 109, 121].

The quick intraoperative measurement of PTH dynamics has significantly altered the approach to parathyroidectomy in the management of primary hyperparathyroidism. In theory, not having to locate the remaining parathyroid glands after identification of an adenoma minimizes the extent of dissection, shortens the operating time, and lowers the risk of inadvertently injuring the recurrent laryngeal nerve or the other normal glands. With piqued patient interest in any surgical technique that can be converted to minimally invasive and with increased surgeon experience utilizing ioPTH, focused parathyroidectomy has rapidly become an attractive alternative to bilateral neck exploration.

Outcome: Comparison of Cure Rates and Complications Following Focused Versus Four-Gland Exploration

Since the mid-1990s, ioPTH has effectively guided an increasing number of surgeons who perform parathyroidectomy. Its popularity has continued to grow with 90% of surgeons practicing a focused parathyroidectomy and 95% of high-volume surgeons using ioPTH monitoring today [140]. It seems that the focused approach with ioPTH monitoring has successfully replaced traditional bilateral cervical exploration in the surgical management of most patients with sporadic primary hyperparathyroidism and positive localization studies. As with any change in tradition, an evaluation of the long-term outcomes is necessary.

Cure Rates

In most studies, operative success is defined as continuous eucalcemia for at least 6 months postoperatively. As mentioned previously, there is an important difference between persistent hyperparathyroidism (i.e., operative failure) and recurrent hyperparathyroidism. Many surgeons believe that focused parathyroidectomy is equally effective in immediately restoring normocalcemia as bilateral neck exploration. Table 21.4 summarizes the results of several studies comparing the operative success of focused exploration using ioPTH with a bilateral approach in the management of primary hyperparathyroidism. Cure rates exceeding 95% are possible with a focused exploration, and these data compare favorably to the reported cure rates after traditional bilateral neck exploration, which also typically range from 95% to 99% [58–65, 70, 133]. When these two operative approaches are compared, there is generally no significant increase in operative success offered by a bilateral approach over a focused one [58, 61, 62, 70, 139, 144, 148, 149]. In fact, a few studies demonstrated a marginally, but significantly, lower rate of persistent hyperparathyroidism in patients undergoing focused parathyroidectomy [60, 133].

The most feared potential problem of the focused exploration is failure to identify multiglandular disease (i.e., a second adenoma or hyperplasia). This risk depends on the percentage of patients with multiglandular disease, the accuracy of localization studies in identifying multiglandular disease, and the accuracy of the ioPTH assay in detecting a residual pathologic parathyroid gland [150]. Studies involving traditional bilateral neck exploration, where parathyroidectomy is guided by surgeon experience and subjective interpretation of gland size as well as gross appearance, have consistently documented an incidence of multiglandular disease ranging from 15% to 30% [111, 112, 114]. However, when gland excision is guided by ioPTH, fewer parathyroid glands are resected with the incidence of multiglandular disease ranging from 4% to 7% [110, 113, 115]. If limitations in localization studies and ioPTH truly miss multiglandular disease in at least 16% of cases at the time of surgery [114], then we would expect focused parathyroidectomy to demonstrate higher rates of persistent hyperparathyroidism. In theory, multiglandular disease should not lead to recurrence because it represents the presence of more than one hypersecreting gland responsible for hypercalcemia at the time of parathyroidectomy. Thus, if all of these glands are not removed, then persistent (not recurrent) hyperparathyroidism will result within 6 months postoperatively [144]. However, as demonstrated in Table 21.4, similar operative failure rates are seen with both techniques.

Despite excellent short-term results with utilization of ioPTH, which are challenging what the incidence of multiglandular disease truly is, some authors that espouse the bilateral approach argue that the low recurrence rates reported for a focused approach are due to a lack of long-term follow-up data. In fact, a concern over focused exploration leaving latent disease behind has led some surgeons to abandon it altogether in favor of a bilateral approach, which has proven durable historically [59]. Now that ioPTH monitoring has been commercially available for nearly 20 years, we have gained more insight into the recurrence rates to be expected from focused parathyroidectomy with this

Table 21.4 Outcomes comparing focused exploration (FE) with ioPTH versus bilateral neck exploration (BNE) for primary hyperparathyroidism (pHPT)

Study [source #]	Procedure	Criterion	Total number of patients	Single gland disease	Multigland disease	Persistent pHPT/ operative failure	Follow-up	Recurrence	Time to recurrence
Irvin et al. [133]	FE with ioPTH	Miami	421	409 (97%)	12 (2.9%)[a]	11 (3%)[a]	n/a	n/a	n/a
	BNE	n/a	340	308 (91%)	32 (9%)[a]	20 (6%)[a]	n/a	n/a	n/a
Grant et al. [70]	FE with ioPTH	Mayo	601	87%[b]	13%[b]	15 (3%)	Mean 25 months[b]	1 (0.2%)	n/a
	BNE	n/a	760	87%[b]	13%[b]	26 (3%)	Mean 25 months[b]	0 (0%)	n/a
Westerdahl et al. [62][c]	FE with ioPTH	≥60% decline from pre-excision value at 15 min post-excision	47	41 (87%)	5 (11%)	2 (4%)	45 (96%) at 1 year 38 (81%) at 5 years	2 (4%)	1 at a year 1 at 5 y
	BNE	n/a	44	40 (91%)	4 (9%)	1 (2%)	43 (97%) at 1 year 33 (75%) at 5 years	1 (2%)	1 at a year
McGill et al. [61]	FE with ioPTH	Miami	405	360 (89%)	45 (11%)[a]	15 (4%)	n/a	n/a	n/a
	BNE	n/a	395	330 (84%)	65 (16%)[a]	9 (2%)	n/a	n/a	n/a
Slepavicius et al. [151][c]	FE with ioPTH	≥50% decline from pre-incision value at 15 mins post-excision	24	21 (87.5%)	3 (12.5%)	0 (0%)	n/a	n/a	n/a
	BNE	n/a	23	21 (91%)	2 (9%)	0 (0%)	n/a	n/a	n/a

(continued)

Table 21.4 (continued)

Study [source #]	Procedure	Criterion	Total number of patients	Single gland disease	Multigland disease	Persistent pHPT/ operative failure	Follow-up	Recurrence	Time to recurrence
Udelsman [60]	FE with ioPTH	Miami	1037	934 (90%)	100 (10%)[a]	6 (0.6%)[a]	Mean 15 months	4 (0.4%)	6.5, 10, 33, 46 months
	BNE	n/a	613	515 (84.0%)	86 (14%)[a]	18 (2.9%)[a]	Mean 36 months	1 (0.2%)	1 at 70 months
Schneider et al. [58]	FE with ioPTH	Wisconsin	1006	– (80.6% overall)	– (19.4% overall)	4 (0.4%)	Median 9 months	25 (2.5%)	Mean 28.1 months
	BNE	n/a	380	– (80.6% overall)	– (19.4% overall)	3 (0.8%)	Median 9 months	8 (2.1%)	Mean 27.2 months

[a]Statistically significant difference
[b]Study did not report single gland disease or multigland disease or follow-up time independently based on the type of procedure performed
[c]Prospective randomized controlled trial

surgical adjunct. Table 21.4 details several reports on recurrent disease following focused parathyroidectomy. The majority of these studies are retrospective in nature as very few prospective randomized control trials [62, 151] have been published specifically comparing focused exploration with ioPTH against bilateral exploration. A review of this data indicates that any "missed" glands, if they were truly undiscovered, require a long period of time (several years in some studies) to become physiologically active. In 2011, Udelsman [60] published his series on 1650 consecutive patients undergoing parathyroidectomy (of which 613 were performed in the standard fashion and 1037 were focused with ioPTH) for sporadic primary hyperparathyroidism. He concluded that a focused parathyroidectomy employing ioPTH is a superior technique offering significant improvements in the cure rate compared to conventional surgery (99.4% vs 97.1%). Schneider et al. [58] recently reported on the long-term results of 1386 parathyroid operations for primary hyperparathyroidism in an attempt to determine whether operative approach (focused exploration with ioPTH or bilateral exploration) influenced disease recurrence. Their conclusion was that neither technique independently predicted recurrence. Age, sex, preoperative PTH level, nonlocalizing sestamibi scan, and the number of glands removed were included in the multivariate analysis but did not independently predict recurrence. However, the percentage decrease in ioPTH was protective against recurrent hyperparathyroidism with the optimal threshold determined to be a decline greater than 63%. Although many surgeons attribute failure to ioPTH, these data underscore the importance of this adjunct, as it was the only factor protective against recurrence for both the entire cohort (which included those undergoing four-gland exploration) and those specifically undergoing a focused exploration [58].

Complications

The routine use of bilateral exploration is not without risk. In theory, when a surgeon does not have to explore the contralateral neck because ioPTH predicts operative success, potential advantages include a lower risk of inadvertently injuring the remaining normal parathyroid glands or the recurrent nerves as well as a decrease in operative time. Although it seems intuitive that complications should occur less frequently with a unilateral approach, this remains a matter of debate. The mortality risk of parathyroidectomy is essentially zero, regardless of which technique is employed. The overall combined perioperative morbidity rate is less than 4% in most reported series, but this rate may be higher in elderly patients receiving general anesthesia [45]. If a single parathyroid gland is explored and resected, then there is no risk of permanent hypoparathyroidism. However, this no longer holds when ioPTH monitoring guides the surgeon to pursue dissection of the contralateral neck. A few studies [60, 64, 152] report a higher incidence of transient hypocalcemia with traditional surgery. Lund University surgeons reported that patients who underwent unilateral neck exploration had a lower incidence of early postoperative hypocalcemia that necessitated calcium supplementation than did those who underwent a bilateral approach. However, there were no significant differences with respect to complication rates between the two groups [64]. Udelsman demonstrated a trend

toward lower rates of postoperative hypocalcemia and recurrent nerve injury with a significant decrease in the overall perioperative complication rate, favoring a focused over a bilateral exploration [60]. Schneider et al. showed that more transient hypocalcemia occurred with a bilateral approach than with focused exploration (1.9% vs 0.1%, respectively). Furthermore, although there was no statistical significance, there was documentation of bleeding and recurrent laryngeal nerve injury within the group that had a bilateral exploration but none of these complications were seen in the group that underwent a focused approach [152].

None of the prospective randomized controlled trials [64, 151, 153] have found a significant difference between focused and bilateral exploration for recurrent nerve injury. Unless specifically documented by postoperative serum calcium levels or progress notes, retrospective reviews relying on patient recall alone may be more likely to miss transient postoperative hypocalcemia and recurrent nerve deficits than randomized prospective controlled trials. Many surgeons also routinely prescribe oral calcium supplementation in the early postoperative period to limit the incidence of symptomatic hypocalcemia, which also minimizes the documentation of this complication. It seems that both approaches are safe and demonstrate minimal, but similar, overall complication rates with the vast majority experiencing an uncomplicated perioperative course.

Other Advantages of a Focused Exploration

Some authors report on the potential benefits of improved cosmesis [151], less pain [151], decreased operative time [154], decreased costs [60, 133, 155], a decreased length of stay [60, 155, 156], and an improved quality of life [156] offered by a focused exploration. Finally, the rare patient who is not cured after a focused exploration can generally undergo a simple, and technically less challenging, second operation that is performed in virgin tissue planes.

Recommendations

Although surgeon judgment and experience remain critical to success in parathyroid surgery, enhancements in preoperative localization techniques along with ioPTH assays have facilitated the treatment of patients with sporadic primary hyperparathyroidism. Specifically, the intraoperative measurement of PTH has been shown to be a valuable tool available to the surgeon during parathyroidectomy and has largely supplanted the subjective evaluation of parathyroid hypersecretion based on gland size. It has enabled a more limited exploration by accurately guiding gland excision and minimizing tissue trauma. There are many large series of focused parathyroid operations guided by ioPTH that have shown excellent, durable cure rates similar to standard four-gland exploration. In fact, some studies have documented the superiority of the focused approach.

When making an evidence-based recommendation regarding the approach to parathyroidectomy based on the literature in Table 21.4, one important criticism is that the overwhelming majority of the data comes from retrospective reviews. This lack of randomization introduces some selection bias. The patients who are undergoing focused exploration in these studies are highly selected and include mainly patients with a positive localization study, no prior neck operations, and no familial component to their primary hyperparathyroidism. On the other hand, series involving the traditional four-gland exploration routinely include complex reoperative cases and multiglandular hyperplasia.

After employing the GRADE method for evaluating the quality of available evidence, we found a lack of high quality data. More long-term data from prospective, randomized controlled trials are necessary to provide even higher-grade evidence in favor of one approach over another. The strength of a recommendation, however, is not necessarily determined by quality of evidence alone. It also relies on other factors, such as risk-benefit ratios, costs, and patient preferences. Thus, we are moderately confident that a focused exploration is a safe, effective technique that is appropriate for most patients with sporadic primary hyperparathyroidism and likely to be comparable to four-gland exploration with regard to cure rates and risk of complications. A specific algorithm for monitoring hormone dynamics so as to accurately predict postoperative eucalcemia is essential. Also, the use of this technique generally requires adequate preoperative imaging and an experienced surgeon. Nevertheless, four-gland exploration remains a valuable technique, especially for those who have familial forms of primary hyperparathyroidism.

References

1. Coker LH, Rorie K, Cantley L, Kirkland K, Stump D, Burbank N, et al. Primary hyperparathyroidism, cognition, and health-related quality of life. Ann Surg. 2005;242(5):642–50.
2. Fraser WD. Hyperparathyroidism. Lancet. 2009;374(9684):145–58.
3. Clark OH, Duh QY. Primary hyperparathyroidism. A surgical perspective. Endocrinol Metab Clin N Am. 1989;18(3):701–14.
4. Wermers RA, Khosla S, Atkinson EJ, Hodgson SF, O'Fallon WM, Melton LJ 3rd. The rise and fall of primary hyperparathyroidism: a population-based study in Rochester, Minnesota, 1965–1992. Ann Intern Med. 1997;126(6):433–40.
5. Heath H 3rd, Hodgson SF, Kennedy MA. Primary hyperparathyroidism. Incidence, morbidity, and potential economic impact in a community. N Engl J Med. 1980;302(4):189–93.
6. Yeh MW, Ituarte PH, Zhou HC, Nishimoto S, Liu IL, Harari A, et al. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. J Clin Endocrinol Metab. 2013;98(3):1122–9.
7. Beard CM, Heath H 3rd, O'Fallon WM, Anderson JA, Earle JD, Melton LJ 3rd. Therapeutic radiation and hyperparathyroidism. A case-control study in Rochester, Minn. Arch Intern Med. 1989;149(8):1887–90.
8. Albright F. A page out of the history of hyperparathyroidism. J Clin Endocrinol Metab. 1948;8(8):637–57.
9. Clark OH, Wilkes W, Siperstein AE, Duh QY. Diagnosis and management of asymptomatic hyperparathyroidism: safety, efficacy, and deficiencies in our knowledge. J Bone Miner Res. 1991;6(Suppl 2):S135–42. discussion 51–2.

10. Turken SA, Cafferty M, Silverberg SJ, De La Cruz L, Cimino C, Lange DJ, et al. Neuromuscular involvement in mild, asymptomatic primary hyperparathyroidism. Am J Med. 1989;87(5):553–7.
11. Bilezikian JP, Brandi ML, Rubin M, Silverberg SJ. Primary hyperparathyroidism: new concepts in clinical, densitometric and biochemical features. J Intern Med. 2005;257(1):6–17.
12. Silverberg SJ, Shane E, Jacobs TP, Siris ES, Gartenberg F, Seldin D, et al. Nephrolithiasis and bone involvement in primary hyperparathyroidism. Am J Med. 1990;89(3):327–34.
13. Silverberg SJ, Bilezikian JP. Asymptomatic primary hyperparathyroidism: a medical perspective. Surg Clin North Am. 2004;84(3):787–801.
14. Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99(10):3561–9.
15. Rao DS, Honasoge M, Divine GW, Phillips ER, Lee MW, Ansari MR, et al. Effect of vitamin D nutrition on parathyroid adenoma weight: pathogenetic and clinical implications. J Clin Endocrinol Metab. 2000;85(3):1054–8.
16. Kandil E, Tufaro AP, Carson KA, Lin F, Somervell H, Farrag T, et al. Correlation of plasma 25-hydroxyvitamin D levels with severity of primary hyperparathyroidism and likelihood of parathyroid adenoma localization on sestamibi scan. Arch Otolaryngol Head Neck Surg. 2008;134(10):1071–5.
17. Silverberg SJ, Clarke BL, Peacock M, Bandeira F, Boutroy S, Cusano NE, et al. Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99(10):3580–94.
18. Silverberg SJ, Shane E, de la Cruz L, Dempster DW, Feldman F, Seldin D, et al. Skeletal disease in primary hyperparathyroidism. J Bone Miner Res. 1989;4(3):283–91.
19. De Geronimo S, Romagnoli E, Diacinti D, D'Erasmo E, Minisola S. The risk of fractures in postmenopausal women with primary hyperparathyroidism. Eur J Endocrinol. 2006;155(3):415–20.
20. Khosla S, Melton LJ 3rd, Wermers RA, Crowson CS, O'Fallon W, Riggs B. Primary hyperparathyroidism and the risk of fracture: a population-based study. J Bone Miner Res. 1999;14(10):1700–7.
21. Larsson K, Ljunghall S, Krusemo UB, Naessen T, Lindh E, Persson I. The risk of hip fractures in patients with primary hyperparathyroidism: a population-based cohort study with a follow-up of 19 years. J Intern Med. 1993;234(6):585–93.
22. Khosla S, Melton J 3rd. Fracture risk in primary hyperparathyroidism. J Bone Miner Res. 2002;17(Suppl 2):N103–7.
23. Rubin MR, Bilezikian JP, McMahon DJ, Jacobs T, Shane E, Siris E, et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. J Clin Endocrinol Metab. 2008;93(9):3462–70.
24. Sorensen MD, Duh QY, Grogan RH, Tran TC, Stoller ML. Urinary parameters as predictors of primary hyperparathyroidism in patients with nephrolithiasis. J Urol. 2012;187(2):516–21.
25. Tassone F, Gianotti L, Emmolo I, Ghio M, Borretta G. Glomerular filtration rate and parathyroid hormone secretion in primary hyperparathyroidism. J Clin Endocrinol Metab. 2009;94(11):4458–61.
26. Yu N, Donnan PT, Flynn RW, Murphy MJ, Smith D, Rudman A, et al. Increased mortality and morbidity in mild primary hyperparathyroid patients. The Parathyroid Epidemiology and Audit Research Study (PEARS). Clin Endocrinol. 2010;73(1):30–4.
27. Yu N, Leese GP, Donnan PT. What predicts adverse outcomes in untreated primary hyperparathyroidism? The Parathyroid Epidemiology and Audit Research Study (PEARS). Clin Endocrinol. 2013;79(1):27–34.
28. Lind L, Hvarfner A, Palmer M, Grimelius L, Akerstrom G, Ljunghall S. Hypertension in primary hyperparathyroidism in relation to histopathology. Eur J Surg. 1991;157(8):457–9.
29. Lind L, Jacobsson S, Palmer M, Lithell H, Wengle B, Ljunghall S. Cardiovascular risk factors in primary hyperparathyroidism: a 15-year follow-up of operated and unoperated cases. J Intern Med. 1991;230(1):29–35.

30. Persson A, Bollerslev J, Rosen T, Mollerup CL, Franco C, Isaksen GA, et al. Effect of surgery on cardiac structure and function in mild primary hyperparathyroidism. Clin Endocrinol. 2011;74(2):174–80.
31. Iwata S, Walker MD, Di Tullio MR, Hyodo E, Jin Z, Liu R, et al. Aortic valve calcification in mild primary hyperparathyroidism. J Clin Endocrinol Metab. 2012;97(1):132–7.
32. Walker MD, Rundek T, Homma S, DiTullio M, Iwata S, Lee JA, et al. Effect of parathyroidectomy on subclinical cardiovascular disease in mild primary hyperparathyroidism. Eur J Endocrinol. 2012;167(2):277–85.
33. Adler JT, Sippel RS, Schaefer S, Chen H. Preserving function and quality of life after thyroid and parathyroid surgery. Lancet Oncol. 2008;9(11):1069–75.
34. Bilezikian JP, Khan AA, Potts JT Jr, Third International Workshop on the Management of Asymptomatic Primary Hyperthyroidism. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. J Clin Endocrinol Metab. 2009;94(2):335–9.
35. Siperstein AE, Shen W, Chan AK, Duh QY, Clark OH. Normocalcemic hyperparathyroidism. Biochemical and symptom profiles before and after surgery. Arch Surg. 1992;127(10):1157–6. discussion 61–3.
36. Silverberg SJ, Bilezikian JP. "Incipient" primary hyperparathyroidism: a "forme fruste" of an old disease. J Clin Endocrinol Metab. 2003;88(11):5348–52.
37. Tordjman KM, Greenman Y, Osher E, Shenkerman G, Stern N. Characterization of normocalcemic primary hyperparathyroidism. Am J Med. 2004;117(11):861–3.
38. Scholz DA, Purnell DC. Asymptomatic primary hyperparathyroidism. 10-year prospective study. Mayo Clin Proc. 1981;56(8):473–8.
39. Rao DS, Wilson RJ, Kleerekoper M, Parfitt AM. Lack of biochemical progression or continuation of accelerated bone loss in mild asymptomatic primary hyperparathyroidism: evidence for biphasic disease course. J Clin Endocrinol Metab. 1988;67(6):1294–8.
40. Silverberg SJ, Brown I, Bilezikian JP. Age as a criterion for surgery in primary hyperparathyroidism. Am J Med. 2002;113(8):681–4.
41. Ambrogini E, Cetani F, Cianferotti L, Vignali E, Banti C, Viccica G, et al. Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective, randomized clinical trial. J Clin Endocrinol Metab. 2007;92(8):3114–21.
42. Bollerslev J, Jansson S, Mollerup CL, Nordenstrom J, Lundgren E, Torring O, et al. Medical observation, compared with parathyroidectomy, for asymptomatic primary hyperparathyroidism: a prospective, randomized trial. J Clin Endocrinol Metab. 2007; 92(5):1687–92.
43. Rao DS, Phillips ER, Divine GW, Talpos GB. Randomized controlled clinical trial of surgery versus no surgery in patients with mild asymptomatic primary hyperparathyroidism. J Clin Endocrinol Metab. 2004;89(11):5415–22.
44. Silverberg SJ, Lewiecki EM, Mosekilde L, Peacock M, Rubin MR. Presentation of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. J Clin Endocrinol Metab. 2009;94(2):351–65.
45. Udelsman R, Akerstrom G, Biagini C, Duh QY, Miccoli P, Niederle B, et al. The surgical management of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99(10):3595–606.
46. Hedback G, Tisell LE, Bengtsson BA, Hedman I, Oden A. Premature death in patients operated on for primary hyperparathyroidism. World J Surg. 1990;14(6):829–35. discussion 36.
47. Ogard CG, Engholm G, Almdal TP, Vestergaard H. Increased mortality in patients hospitalized with primary hyperparathyroidism during the period 1977–1993 in Denmark. World J Surg. 2004;28(1):108–11.
48. Sivula A, Pelkonen R. Long-term health risk of primary hyperparathyroidism: the effect of surgery. Ann Med. 1996;28(2):95–100.
49. Ronni-Sivula H. Causes of death in patients previously operated on for primary hyperparathyroidism. Ann Chir Gynaecol. 1985;74(1):13–8.
50. Bostrom H, Alveryd A. Stroke in hyperparathyroidism. Acta Med Scand. 1972;192(4):299–308.

51. Palmer M, Adami HO, Bergstrom R, Akerstrom G, Ljunghall S. Mortality after surgery for primary hyperparathyroidism: a follow-up of 441 patients operated on from 1956 to 1979. Surgery. 1987;102(1):1–7.
52. Yeh MW, Wiseman JE, Ituarte PH, Pasternak JD, Hwang RS, Wu B, et al. Surgery for primary hyperparathyroidism: are the consensus guidelines being followed? Ann Surg. 2012;255(6):1179–83.
53. Mandel F. Therapeutisher Versuch bein Einem Falls von Ostitis Fibrosa Generalisata Mittles: Extirpation eins Epithelkorperchen Tumors. Wein Klin Wochenshr Zentral. 1926; 143:245–84.
54. Kebebew E, Arici C, Duh QY, Clark OH. Localization and reoperation results for persistent and recurrent parathyroid carcinoma. Arch Surg. 2001;136(8):878–85.
55. Jaskowiak N, Norton JA, Alexander HR, Doppman JL, Shawker T, Skarulis M, et al. A prospective trial evaluating a standard approach to reoperation for missed parathyroid adenoma. Ann Surg. 1996;224(3):308–20. discussion 20–1.
56. Shen W, Duren M, Morita E, Higgins C, Duh QY, Siperstein AE, et al. Reoperation for persistent or recurrent primary hyperparathyroidism. Arch Surg. 1996;131(8):861–7. discussion 7–9.
57. Bruining HA, Birkenhager JC, Ong GL, Lamberts SW. Causes of failure in operations for hyperparathyroidism. Surgery. 1987;101(5):562–5.
58. Schneider DF, Mazeh H, Chen H, Sippel RS. Predictors of recurrence in primary hyperparathyroidism: an analysis of 1386 cases. Ann Surg. 2014;259(3):563–8.
59. Norman J, Lopez J, Politz D. Abandoning unilateral parathyroidectomy: why we reversed our position after 15,000 parathyroid operations. J Am Coll Surg. 2012;214(3):260–9.
60. Udelsman R, Lin Z, Donovan P. The superiority of minimally invasive parathyroidectomy based on 1650 consecutive patients with primary hyperparathyroidism. Ann Surg. 2011;253(3):585–91.
61. McGill J, Sturgeon C, Kaplan SP, Chiu B, Kaplan EL, Angelos P. How does the operative strategy for primary hyperparathyroidism impact the findings and cure rate? A comparison of 800 parathyroidectomies. J Am Coll Surg. 2008;207(2):246–9.
62. Westerdahl J, Bergenfelz A. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: five-year follow-up of a randomized controlled trial. Ann Surg. 2007;246(6):976–80. discussion 80–1.
63. Allendorf J, DiGorgi M, Spanknebel K, Inabnet W, Chabot J, Logerfo P. 1112 consecutive bilateral neck explorations for primary hyperparathyroidism. World J Surg. 2007;31(11):2075–80.
64. Bergenfelz A, Lindblom P, Tibblin S, Westerdahl J. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: a prospective randomized controlled trial. Ann Surg. 2002;236(5):543–51.
65. van Heerden JA, Grant CS. Surgical treatment of primary hyperparathyroidism: an institutional perspective. World J Surg. 1991;15(6):688–92.
66. Clark OH, Way LW, Hunt TK. Recurrent hyperparathyroidism. Ann Surg. 1976;184(4):391–402.
67. Cooke TJ, Boey JH, Sweeney EC, Gilbert JM, Taylor S. Parathyroidectomy: extent of resection and late results. Br J Surg. 1977;64(3):153–7.
68. Rudberg C, Akerstrom G, Palmer M, Ljunghall S, Adami HO, Johansson H, et al. Late results of operation for primary hyperparathyroidism in 441 patients. Surgery. 1986;99(6):643–51.
69. Tibblin S, Bizard JP, Bondeson AG, Bonjer J, Bruining HA, Meier F, et al. Primary hyperparathyroidism due to solitary adenoma. A comparative multicentre study of early and long-term results of different surgical regimens. Eur J Surg. 1991;157(9):511–5.
70. Grant CS, Thompson G, Farley D, van Heerden J. Primary hyperparathyroidism surgical management since the introduction of minimally invasive parathyroidectomy: Mayo Clinic experience. Arch Surg. 2005;140(5):472–8. discussion 8–9.
71. Malmaeus J, Granberg PO, Halvorsen J, Akerstrom G, Johansson H. Parathyroid surgery in Scandinavia. Acta Chir Scand. 1988;154(7–8):409–13.

72. Snyder SK, Lairmore TC, Hendricks JC, Roberts JW. Elucidating mechanisms of recurrent laryngeal nerve injury during thyroidectomy and parathyroidectomy. J Am Coll Surg. 2008;206(1):123–30.
73. Chen H. Radioguided parathyroid surgery. Adv Surg. 2004;38:377–92.
74. Wang CA. Surgical management of primary hyperparathyroidism. Curr Probl Surg. 1985;22(11):1–50.
75. Tibblin S, Bondeson AG, Ljungberg O. Unilateral parathyroidectomy in hyperparathyroidism due to single adenoma. Ann Surg. 1982;195(3):245–52.
76. Doppman JL. Reoperative parathyroid surgery; localization procedures. Prog Surg. 1986;18:117–32.
77. Clark OH. Surgical treatment of primary hyperparathyroidism. Adv Endocrinol Metab. 1995;6:1–16.
78. Kunstman JW, Kirsch JD, Mahajan A, Udelsman R. Clinical review: parathyroid localization and implications for clinical management. J Clin Endocrinol Metab. 2013;98(3):902–12.
79. Sample WF, Mitchell SP, Bledsoe RC. Parathyroid ultrasonography. Radiology. 1978;127(2):485–90.
80. Arima M, Yokoi H, Sonoda T. Preoperative identification of tumor of the parathyroid by ultrasonotomography. Surg Gynecol Obstet. 1975;141(2):242–4.
81. Lucas RJ, Welsh RJ, Glover JL. Unilateral neck exploration for primary hyperparathyroidism. Arch Surg. 1990;125(8):982–4. discussion 4–5.
82. Rickes S, Sitzy J, Neye H, Ocran KW, Wermke W. High-resolution ultrasound in combination with colour-Doppler sonography for preoperative localization of parathyroid adenomas in patients with primary hyperparathyroidism. Ultraschall Med. 2003;24(2):85–9.
83. Cheung K, Wang TS, Farrokhyar F, Roman SA, Sosa JA. A meta-analysis of preoperative localization techniques for patients with primary hyperparathyroidism. Ann Surg Oncol. 2012;19(2):577–83.
84. Ruda JM, Hollenbeak CS, Stack BC Jr. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. Otolaryngol Head Neck Surg. 2005;132(3):359–72.
85. Berber E, Parikh RT, Ballem N, Garner CN, Milas M, Siperstein AE. Factors contributing to negative parathyroid localization: an analysis of 1000 patients. Surgery. 2008;144(1):74–9.
86. Bentrem DJ, Angelos P, Talamonti MS, Nayar R. Is preoperative investigation of the thyroid justified in patients undergoing parathyroidectomy for hyperparathyroidism? Thyroid. 2002;12(12):1109–12.
87. Prager G, Czerny C, Ofluoglu S, Kurtaran A, Passler C, Kaczirek K, et al. Impact of localization studies on feasibility of minimally invasive parathyroidectomy in an endemic goiter region. J Am Coll Surg. 2003;196(4):541–8.
88. Milas M, Mensah A, Alghoul M, Berber E, Stephen A, Siperstein A, et al. The impact of office neck ultrasonography on reducing unnecessary thyroid surgery in patients undergoing parathyroidectomy. Thyroid. 2005;15(9):1055–9.
89. Morita SY, Somervell H, Umbricht CB, Dackiw AP, Zeiger MA. Evaluation for concomitant thyroid nodules and primary hyperparathyroidism in patients undergoing parathyroidectomy or thyroidectomy. Surgery. 2008;144(6):862–6. discussion 6–8.
90. De Feo ML, Colagrande S, Biagini C, Tonarelli A, Bisi G, Vaggelli L, et al. Parathyroid glands: combination of (99m)Tc MIBI scintigraphy and US for demonstration of parathyroid glands and nodules. Radiology. 2000;214(2):393–402.
91. Haber RS, Kim CK, Inabnet WB. Ultrasonography for preoperative localization of enlarged parathyroid glands in primary hyperparathyroidism: comparison with (99m)technetium sestamibi scintigraphy. Clin Endocrinol. 2002;57(2):241–9.
92. Reeder SB, Desser TS, Weigel RJ, Jeffrey RB. Sonography in primary hyperparathyroidism: review with emphasis on scanning technique. J Ultrasound Med. 2002;21(5):539–52. quiz 53–4.
93. Gilat H, Cohen M, Feinmesser R, Benzion J, Shvero J, Segal K, et al. Minimally invasive procedure for resection of a parathyroid adenoma: the role of preoperative high-resolution ultrasonography. J Clin Ultrasound. 2005;33(6):283–7.

94. Young AE, Gaunt JI, Croft DN, Collins RE, Wells CP, Coakley AJ. Location of parathyroid adenomas by thallium-201 and technetium-99m subtraction scanning. Br Med J. 1983;286(6375):1384–6.
95. Coakley AJ, Kettle AG, Wells CP, O'Doherty MJ, Collins RE. 99Tcm sestamibi—a new agent for parathyroid imaging. Nucl Med Commun. 1989;10(11):791–4.
96. Gotthardt M, Lohmann B, Behr TM, Bauhofer A, Franzius C, Schipper ML, et al. Clinical value of parathyroid scintigraphy with technetium-99m methoxyisobutylisonitrile: discrepancies in clinical data and a systematic metaanalysis of the literature. World J Surg. 2004;28(1):100–7.
97. Mihai R, Gleeson F, Buley ID, Roskell DE, Sadler GP. Negative imaging studies for primary hyperparathyroidism are unavoidable: correlation of sestamibi and high-resolution ultrasound scanning with histological analysis in 150 patients. World J Surg. 2006;30(5):697–704.
98. Erbil Y, Barbaros U, Yanik BT, Salmaslioglu A, Tunaci M, Adalet I, et al. Impact of gland morphology and concomitant thyroid nodules on preoperative localization of parathyroid adenomas. Laryngoscope. 2006;116(4):580–5.
99. Vattimo A, Bertelli P, Cintorino M, Burroni L, Volterrani D, Vella A, et al. Hurthle cell tumor dwelling in hot thyroid nodules: preoperative detection with technetium-99m-MIBI dual-phase scintigraphy. Journal of nuclear medicine : official publication. Soc Nucl Med. 1998;39(5):822–5.
100. Siperstein A, Berber E, Mackey R, Alghoul M, Wagner K, Milas M. Prospective evaluation of sestamibi scan, ultrasonography, and rapid PTH to predict the success of limited exploration for sporadic primary hyperparathyroidism. Surgery. 2004;136(4):872–80.
101. Wong KK, Fig LM, Gross MD, Dwamena BA. Parathyroid adenoma localization with 99mTc-sestamibi SPECT/CT: a meta-analysis. Nucl Med Commun. 2015;36(4):363–75.
102. Lavely WC, Goetze S, Friedman KP, Leal JP, Zhang Z, Garret-Mayer E, et al. Comparison of SPECT/CT, SPECT, and planar imaging with single- and dual-phase (99m)Tc-sestamibi parathyroid scintigraphy. Journal of nuclear medicine : official publication. Soc Nucl Med. 2007;48(7):1084–9.
103. Mortenson MM, Evans DB, Lee JE, Hunter GJ, Shellingerhout D, Vu T, et al. Parathyroid exploration in the reoperative neck: improved preoperative localization with 4D-computed tomography. J Am Coll Surg. 2008;206(5):888–95. discussion 95–6.
104. Starker LF, Mahajan A, Bjorklund P, Sze G, Udelsman R, Carling T. 4D parathyroid CT as the initial localization study for patients with de novo primary hyperparathyroidism. Ann Surg Oncol. 2011;18(6):1723–8.
105. Mahajan A, Starker LF, Ghita M, Udelsman R, Brink JA, Carling T. Parathyroid four-dimensional computed tomography: evaluation of radiation dose exposure during preoperative localization of parathyroid tumors in primary hyperparathyroidism. World J Surg. 2012;36(6):1335–9.
106. Patel CN, Salahudeen HM, Lansdown M, Scarsbrook AF. Clinical utility of ultrasound and 99mTc sestamibi SPECT/CT for preoperative localization of parathyroid adenoma in patients with primary hyperparathyroidism. Clin Radiol. 2010;65(4):278–87.
107. Chiu B, Sturgeon C, Angelos P. What is the link between nonlocalizing sestamibi scans, multigland disease, and persistent hypercalcemia? A study of 401 consecutive patients undergoing parathyroidectomy. Surgery. 2006;140(3):418–22.
108. Arici C, Cheah WK, Ituarte PH, Morita E, Lynch TC, Siperstein AE, et al. Can localization studies be used to direct focused parathyroid operations? Surgery. 2001;129(6):720–9.
109. Sugg SL, Krzywda EA, Demeure MJ, Wilson SD. Detection of multiple gland primary hyperparathyroidism in the era of minimally invasive parathyroidectomy. Surgery. 2004;136(6):1303–9.
110. Carneiro DM, Solorzano CC, Nader MC, Ramirez M, Irvin GL 3rd. Comparison of intraoperative iPTH assay (QPTH) criteria in guiding parathyroidectomy: which criterion is the most accurate? Surgery. 2003;134(6):973–9. discussion 9–81.
111. Haciyanli M, Lal G, Morita E, Duh QY, Kebebew E, Clark OH. Accuracy of preoperative localization studies and intraoperative parathyroid hormone assay in patients with primary hyperparathyroidism and double adenoma. J Am Coll Surg. 2003;197(5):739–46.

112. Clerici T, Brandle M, Lange J, Doherty GM, Gauger PG. Impact of intraoperative parathyroid hormone monitoring on the prediction of multiglandular parathyroid disease. World J Surg. 2004;28(2):187–92.
113. Riss P, Kaczirek K, Heinz G, Bieglmayer C, Niederle B. A "defined baseline" in PTH monitoring increases surgical success in patients with multiple gland disease. Surgery. 2007;142(3):398–404.
114. Siperstein A, Berber E, Barbosa GF, Tsinberg M, Greene AB, Mitchell J, et al. Predicting the success of limited exploration for primary hyperparathyroidism using ultrasound, sestamibi, and intraoperative parathyroid hormone: analysis of 1158 cases. Ann Surg. 2008;248(3):420–8.
115. Barczynski M, Konturek A, Hubalewska-Dydejczyk A, Cichon S, Nowak W. Evaluation of Halle, Miami, Rome, and Vienna intraoperative iPTH assay criteria in guiding minimally invasive parathyroidectomy. Langenbeck's Arch Surg. 2009;394(5):843–9.
116. Kaplan EL, Yashiro T, Salti G. Primary hyperparathyroidism in the 1990s. Choice of surgical procedures for this disease. Ann Surg. 1992;215(4):300–17.
117. Molinari AS, Irvin GL 3rd, Deriso GT, Bott L. Incidence of multiglandular disease in primary hyperparathyroidism determined by parathyroid hormone secretion. Surgery. 1996;120(6):934–6. discussion 6–7.
118. Westerdahl J, Lindblom P, Bergenfelz A. Measurement of intraoperative parathyroid hormone predicts long-term operative success. Arch Surg. 2002;137(2):186–90.
119. Vignali E, Picone A, Materazzi G, Steffe S, Berti P, Cianferotti L, et al. A quick intraoperative parathyroid hormone assay in the surgical management of patients with primary hyperparathyroidism: a study of 206 consecutive cases. Eur J Endocrinol. 2002; 146(6):783–8.
120. Westerdahl J, Bergenfelz A. Sestamibi scan-directed parathyroid surgery: potentially high failure rate without measurement of intraoperative parathyroid hormone. World J Surg. 2004;28(11):1132–8.
121. Carneiro-Pla DM, Solorzano CC, Irvin GL 3rd. Consequences of targeted parathyroidectomy guided by localization studies without intraoperative parathyroid hormone monitoring. J Am Coll Surg. 2006;202(5):715–22.
122. Norman J. Recent trends becoming standard of care yielding smaller, more successful operations at a lower cost. Otolaryngol Clin N Am. 2004;37(4):683–8. vii.
123. Chen H, Mack E, Starling JR. Radioguided parathyroidectomy is equally effective for both adenomatous and hyperplastic glands. Ann Surg. 2003;238(3):332–7. discussion 7–8.
124. Nussbaum SR, Thompson AR, Hutcheson KA, Gaz RD, Wang CA. Intraoperative measurement of parathyroid hormone in the surgical management of hyperparathyroidism. Surgery. 1988;104(6):1121–7.
125. Irvin GL 3rd, Dembrow VD, Prudhomme DL. Operative monitoring of parathyroid gland hyperfunction. Am J Surg. 1991;162(4):299–302.
126. James BC, Nagar S, Tracy M, Kaplan EL, Angelos P, Scherberg NH, et al. A novel, ultrarapid parathyroid hormone assay to distinguish parathyroid from nonparathyroid tissue. Surgery. 2014;156(6):1638–43.
127. Irvin GL 3rd, Dembrow VD, Prudhomme DL. Clinical usefulness of an intraoperative "quick parathyroid hormone" assay. Surgery. 1993;114(6):1019–22. discussion 22–3.
128. Mazeh H, Chen H, Leverson G, Sippel RS. Creation of a "Wisconsin index" nomogram to predict the likelihood of additional hyperfunctioning parathyroid glands during parathyroidectomy. Ann Surg. 2013;257(1):138–41.
129. Kebebew E, Hwang J, Reiff E, Duh QY, Clark OH. Predictors of single-gland vs multigland parathyroid disease in primary hyperparathyroidism: a simple and accurate scoring model. Arch Surg. 2006;141(8):777–82. discussion 82.
130. Riss P, Kaczirek K, Bieglmayer C, Niederle B. PTH spikes during parathyroid exploration--a possible pitfall during PTH monitoring? Langenbeck's Arch Surg. 2007;392(4):427–30.
131. Chiu B, Sturgeon C, Angelos P. Which intraoperative parathyroid hormone assay criterion best predicts operative success? A study of 352 consecutive patients. Arch Surg. 2006;141(5):483–7. discussion 7–8.

132. Cook MR, Pitt SC, Schaefer S, Sippel R, Chen H. A rising ioPTH level immediately after parathyroid resection: are additional hyperfunctioning glands always present? An application of the Wisconsin criteria. Ann Surg. 2010;251(6):1127–30.
133. Irvin GL 3rd, Solorzano CC, Carneiro DM. Quick intraoperative parathyroid hormone assay: surgical adjunct to allow limited parathyroidectomy, improve success rate, and predict outcome. World J Surg. 2004;28(12):1287–92.
134. Lombardi CP, Raffaelli M, Traini E, Di Stasio E, Carrozza C, De Crea C, et al. Intraoperative PTH monitoring during parathyroidectomy: the need for stricter criteria to detect multiglandular disease. Langenbeck's Arch Surg. 2008;393(5):639–45.
135. Weber KJ, Misra S, Lee JK, Wilhelm SW, DeCresce R, Prinz RA. Intraoperative PTH monitoring in parathyroid hyperplasia requires stricter criteria for success. Surgery. 2004;136(6):1154–9.
136. Jaskowiak NT, Sugg SL, Helke J, Koka MR, Kaplan EL. Pitfalls of intraoperative quick parathyroid hormone monitoring and gamma probe localization in surgery for primary hyperparathyroidism. Arch Surg. 2002;137(6):659–68. discussion 68–9.
137. Gauger PG, Agarwal G, England BG, Delbridge LW, Matz KA, Wilkinson M, et al. Intraoperative parathyroid hormone monitoring fails to detect double parathyroid adenomas: a 2-institution experience. Surgery. 2001;130(6):1005–10.
138. Lew JI, Irvin GL 3rd. Focused parathyroidectomy guided by intra-operative parathormone monitoring does not miss multiglandular disease in patients with sporadic primary hyperparathyroidism: a 10-year outcome. Surgery. 2009;146(6):1021–7.
139. Lew JI, Rivera M, Irvin GL 3rd, Solorzano CC. Operative failure in the era of focused parathyroidectomy: a contemporary series of 845 patients. Arch Surg. 2010;145(7):628–33.
140. Richards ML, Thompson GB, Farley DR, Grant CS. An optimal algorithm for intraoperative parathyroid hormone monitoring. Arch Surg. 2011;146(3):280–5.
141. Richards ML, Grant CS. Current applications of the intraoperative parathyroid hormone assay in parathyroid surgery. Am Surg. 2007;73(4):311–7.
142. Hughes DT, Miller BS, Doherty GM, Gauger PG. Intraoperative parathyroid hormone monitoring in patients with recognized multiglandular primary hyperparathyroidism. World J Surg. 2011;35(2):336–41.
143. Carneiro-Pla DM, Solorzano CC, Lew JI, Irvin GL 3rd. Long-term outcome of patients with intraoperative parathyroid level remaining above the normal range during parathyroidectomy. Surgery. 2008;144(6):989–93. discussion 93–4.
144. Carneiro DM, Solorzano CC, Irvin GL 3rd. Recurrent disease after limited parathyroidectomy for sporadic primary hyperparathyroidism. J Am Coll Surg. 2004;199(6):849–53. discussion 53–5.
145. Carneiro DM, Irvin GL 3rd. Late parathyroid function after successful parathyroidectomy guided by intraoperative hormone assay (QPTH) compared with the standard bilateral neck exploration. Surgery. 2000;128(6):925–9. discussion 35–6.
146. Barczynski M, Golkowski F, Nawrot I. The current status of intraoperative iPTH assay in surgery for primary hyperparathyroidism. Gland Surg. 2015;4(1):36–43.
147. Stalberg P, Sidhu S, Sywak M, Robinson B, Wilkinson M, Delbridge L. Intraoperative parathyroid hormone measurement during minimally invasive parathyroidectomy: does it "value-add" to decision-making? J Am Coll Surg. 2006;203(1):1–6.
148. Chen H, Pruhs Z, Starling JR, Mack E. Intraoperative parathyroid hormone testing improves cure rates in patients undergoing minimally invasive parathyroidectomy. Surgery. 2005;138(4):583–7. discussion 7–90.
149. Venkat R, Kouniavsky G, Tufano RP, Schneider EB, Dackiw AP, Zeiger MA. Long-term outcome in patients with primary hyperparathyroidism who underwent minimally invasive parathyroidectomy. World J Surg. 2012;36(1):55–60.
150. Proye CA, Carnaille B, Bizard JP, Quievreux JL, Lecomte-Houcke M. Multiglandular disease in seemingly sporadic primary hyperparathyroidism revisited: where are we in the early 1990s? A plea against unilateral parathyroid exploration. Surgery. 1992;112(6):1118–22.

151. Slepavicius A, Beisa V, Janusonis V, Strupas K. Focused versus conventional parathyroidectomy for primary hyperparathyroidism: a prospective, randomized, blinded trial. Langenbeck's Arch Surg. 2008;393(5):659–66.
152. Schneider DF, Mazeh H, Sippel RS, Chen H. Is minimally invasive parathyroidectomy associated with greater recurrence compared to bilateral exploration? Analysis of more than 1,000 cases. Surgery. 2012;152(6):1008–15.
153. Miccoli P, Bendinelli C, Berti P, Vignali E, Pinchera A, Marcocci C. Video-assisted versus conventional parathyroidectomy in primary hyperparathyroidism: a prospective randomized study. Surgery. 1999;126(6):1117–21. discussion 21–2.
154. Irvin GL 3rd, Sfakianakis G, Yeung L, Deriso GT, Fishman LM, Molinari AS, et al. Ambulatory parathyroidectomy for primary hyperparathyroidism. Arch Surg. 1996;131(10):1074–8.
155. Chen H, Sokoll LJ, Udelsman R. Outpatient minimally invasive parathyroidectomy: a combination of sestamibi-SPECT localization, cervical block anesthesia, and intraoperative parathyroid hormone assay. Surgery. 1999;126(6):1016–21. discussion 21–2.
156. Adler JT, Sippel RS, Chen H. The influence of surgical approach on quality of life after parathyroid surgery. Ann Surg Oncol. 2008;15(6):1559–65.