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Imaging techniques in parathyroid surgery for primary hyperparathyroidism

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Abstract

As more patients present with the incidental diagnosis of primary hyperparathyroidism due to biochemical screening, treatment guidelines have been developed for the treatment of hyperparathyroidism. Management of primary hyperparathyroidism has evolved in recent years with considerable interest in minimally invasive approaches. Successful localization of the diseased gland(s) by nuclear imaging and anatomical studies along with rapid intraoperative parathyroid hormone assay has allowed for focused and minimally invasive surgical approaches. Patients in whom the localization studies have identified single gland adenoma or unilateral disease are candidates for such focused approaches instead of the traditional approach of bilateral exploration. These imaging techniques have also been critical in the successful management of patients with persistent or recurrent disease.

Keywords

hyperparathyroidism; sestamibi; endoscopic exploration; minimally invasive single-gland exploration; parathyroid hormone assays

Introduction

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia, the treatment of which is primarily surgical resection. PHPT is characterized by hypercalcemia due to over production of parathyroid hormone (PTH). In the Western world as a result of increasing biochemical screening, it has evolved from the disease of “bones, moans stones and groans” to a disorder that is most commonly asymptomatic in many patients [1, 2]. PHPT is a common disease occurring in about 1% of the adults and incidence rises to 2% or more in population older than 55 years [3]. It is 2-3 times more common in women than men and peaks around the fourth and fifth decade of life [1, 4]. The traditional approach to parathyroid surgery consists of bilateral neck exploration with the goal of identifying and visually inspecting all four parathyroid glands. The success of this approach exceeds 90 to 95%. However, cervical exploration requires a larger incision, longer operating time and potentially can have higher morbidity. Because more than 85% of patients with primary hyperparathyroidism have a single gland adenoma, four gland exploration may not be necessary in majority of the patients if the enlarged parathyroid gland can be identified and

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localized preoperatively. There has been considerable interest in localization studies of the abnormal parathyroid gland(s) since the 1980s. The goal of this approach is to allow the surgeon to perform minimally invasive parathyroidectomy. The minimally invasive approach includes small incision parathyroidectomy, out-patient parathyroidectomy, endoscopic or video assisted parathyroidectomy and parathyroidectomy under local anesthesia. Various invasive and non-invasive localizing tests are available for evaluating PHPT. The traditional non-invasive imaging modalities include ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI); however, more recently, technetium 99m sestamibi scan and technetium 99m sestamibi single emission computed tomography (Tc99m-MIBI-SPECT) have been utilized for localizing the pathologic or enlarged parathyroid glands.

In this paper, we will review the pertinent anatomy, pathophysiology of the parathyroid glands and diagnosis of primary hyperparathyroidism. The indications for the management of hyperparathyroidism and treatment options will be reviewed. Furthermore, we will discuss various surgical approaches to parathyroid surgery. In detail, we will review the role of various preoperative localization techniques and the sensitivity and specificity of each technique in localizing the abnormal parathyroid gland and the concordance of this identification with the operative and pathologic findings. Additionally, we will evaluate the role of intra operative parathormone assay in determining the success of the image guided minimally invasive approach.

Anatomy and Embryology of Parathyroid Glands

The parathyroid glands are endodermal in origin and develop from the dorsal wing of the third and fourth pharyngeal pouches [5, 6]. The first detailed anatomic description of the parathyroid glands was published by Welsh in 1898 and subsequently by Halstead and Evans in 1907 making a distinction between the superior and the inferior glands [7, 8]. They produce parathyroid hormone (PTH) which regulates the circulating level of calcium through intestinal and renal absorption and bone remodeling. There are typically four parathyroid glands; however, supernumerary glands and less than four glands have been reported. In a reported series of 428 cases, 0.5% had 6 glands, 25% had five glands, 87% had four glands, and 6.1% of the cases had three glands [9]. The majority of the supernumerary glands were either rudimentary or divided weighing as little as less than 5mg and in close proximity of a normal gland. The normal weight of each parathyroid gland is about 35 to 40mg and measuring about 3-8 mm [9, 10]. The inferior thyroid artery is the predominant vascular supply to both upper and lower parathyroid glands in 76% to 86% of the cases [9].

The superior parathyroid glands originate from the fourth pharyngeal pouch. As they lose their attachment with the pharyngeal wall, they attach to the posterior surface of the inferiorly migrating thyroid [5, 10]. They have much shorter migration distance compared to the inferior parathyroid glands accounting for their more predictable location. They are generally at the level of the upper two thirds of the thyroid. In an autopsy study of 503 cases, 80% of the superior glands were located on the posterior aspect of the thyroid gland within a circumscribed area 2cm in diameter about 1cm above the crossing point of the recurrent laryngeal nerve and inferior thyroid artery [11]. In this study, the ectopic superior parathyroid glands were found at the level of the upper pole of the thyroid and above the pole in 2% and 0.8% of the subjects respectively. Other ectopic positions of superior parathyroid glands such as in the posterior neck, retropharyngeal, retroesophageal space and intrathyroidal position are quite rare and reported in up to 1% of the cases[11, 12].

While the dorsal wing of the third pharyngeal pouch gives rise to the inferior parathyroid glands, the ventral wing gives rise to the thymus during the fifth week of gestation [5]. Both primitive glands lose their connection with the pharyngeal wall, and join the thymus as it travels caudally and medially to its final position in the mediastinum [5, 13]. This migration of the inferior parathyroid glands with the thymus results in the inferior parathyroid gland to be in a plane that is usually ventral to that of the superior parathyroid glands [13]. For the same reason, ectopic inferior parathyroid glands can be found anywhere along this large area of descent up to the superior border of the pericardium [14]. In a study of 645 parathyroid glands from 160 post mortem subjects, the inferior glands were evenly distributed between the lower pole of the thyroid and isthmus [12]. In this study, 42% of the inferior parathyroid glands were found on the anterior or the postero-lateral surface of the lower pole of the thyroid while 39% were located in the lower neck in proximity to the thymic tissue, 15% lateral to the thyroid and only 2% within the mediastinal thymic tissue. The persistence of the primitive attachment of the inferior parathyroid glands to the thymus, during the thymic migration, may result in a more inferior placement of the parathyroid glands. In this situation, the inferior parathyroid glands may be found at the level of the anterior superior mediastinum in close proximity to the upper pole of thymic remnants [15]. Exploration of the superior mediastinum becomes important during four gland exploration when the inferior parathyroid glands cannot be identified in the neck.

A rare ectopic location that could be a source of pitfall during parathyroid surgery for hyperparathyroidism is the intrathyroid location of the parathyroid glands. The embryologic origin of this ectopic location has been controversial, but they have been reported to originate from either the superior or the inferior glands [11, 16-18]. The incidence of intrathyroid parathyroid gland is reported between 0.7% and 3.6% in the literature [17, 19, 20]. Due to their rarity, the intrathyroid parathyroid glands can be missed by preoperative imaging. This must be kept in mind when meticulous bilateral neck exploration fails to identify the hyperfunctioning gland. However, most of the time, the enlarged parathyroid glands are in the capsule of the thyroid or in the crypts of the thyroid tissue and are missed as intra-thyroid parathyroid. In majority of the cases, parathyroid glands are located in symmetrical position in the neck. In one study, symmetrical position of the superior and inferior glands in 80% and 70% of the cases, respectively, with a relative symmetry of 60% for all four glands [11].

Etiology

The most challenging aspect of managing patients with PHPT is the recognition of the pathologic process that gives rise to the disorder. The appropriate treatment choice is directly dependent on underlying etiology of the disorder. PHPT could be due to adenoma, four gland hyperplasia and rarely due to carcinoma. Most adults (80% to 85%) with PHPT have single benign parathyroid adenoma and up to 4% to 5% are reported to have double adenomas [21, 22]. Four gland hyperplasia is reported in up to 15% of patients with primary hyperparathyroidism and parathyroid carcinoma in 0.8% to 2% of the cases [23, 24]. In the MEN-1 and MEN-2 and the familial syndromes, hyperplasia is the primary etiology of the hyperparathyroidism. Classically, an adenoma is defined as a pathologically enlarged gland with a rim of normal tissue that is most commonly solitary. Many surgeons and pathologists agree that differentiating adenoma from hyperplasia on frozen section is extremely difficult and it can primarily be used to distinguish parathyroid tissue from other tissue; however routine biopsy of the parathyroid glands is not recommended [18, 25]. Additionally criteria, such as gland size, shape, and cell density and type, have been shown to be of little help in distinguishing between adenoma and hyperplasia [26].

Pathophysiology

Parathyroid glands secrete parathyroid hormone (PTH) that is the key regulator of calcium homeostasis. PTH is secreted as an 84-amino acid peptide with a short plasma half-life (2–4 minutes). It is metabolized to biologically active N-terminal and inactive C-terminal fragments. The major regulator of PTH levels is the extracellular calcium through a feedback mechanism control of the calcium receptor [27]. Calcitriol or 1,25-dihydroxyvitamin D (1,25-(OH)₂D) is the other essential mediator of calcium homeostasis, the synthesis of which is regulated by PTH. Calcitriol production begins when cholecalciferol (vitamin D) is generated in skin exposed to ultraviolet light or absorbed through the intestine. In the liver, vitamin D is hydroxylated to 25-(OH)D and converted 1,25-(OH)₂D₃ (calcitriol) in the kidneys. This last step is tightly regulated by PTH [28]. PTH and calcitriol act through the gastrointestinal tract, bone, and the kidney to maintain circulating ionized calcium concentrations. PTH increases serum calcium by acting indirectly on the osteoclasts in the skeleton to promote bone resorption and thus release of calcium into extracellular fluid. In addition to regulating calcitriol production, PTH also enhances calcium resorption at the distal nephron of the kidney. Through this series of checks and balances, extracellular calcium concentration is carefully maintained in the body and at times at the expense of skeletal calcium stores [29].

Diagnosis

PHPT is usually diagnosed by the clinician because of hypercalcemia found on routine laboratory evaluation with an inappropriately elevated or normal levels of PTH [30]. Patients with PHPT typically have low phosphorus, because elevated PTH levels decrease the resorption of phosphorus in the kidneys. Most commonly, these patients are asymptomatic; however, a careful history and physical examination is necessary to rule out other causes of hypercalcemia. Although PHPT is the most common cause of hypercalcemia in the ambulatory setting, the differential diagnosis of hypercalcemia is complex and includes conditions such as metastatic cancer, multiple myeloma, sarcoidosis and other granulomatous diseases, ingestion of calcium or vitamin D, milk-alkali syndrome, and other less common causes. In addition to PHPT, other disorders such as familial hypocalciuric hypercalcemia (FHH) will result in elevated levels of PTH and calcium. However, 24 hour urine calcium will show abnormally low levels of calcium in the urine in patients with FHH. Medications such as thiazides and lithium can result in elevation of PTH and calcium levels. Patients with tertiary hyperparathyroidism, who had a history of renal failure and subsequent renal transplantation, will also have elevated levels of PTH and calcium.

PTH levels are measured using immunoradiometric assays. The intact PTH assay that measures the PTH 1-84 and the non-PTH 1-84 and the bioactive assay that measures the PTH 1-84 and N-terminal PTH can be used for the diagnosis of PHPT with excellent correlation [31-33]. Plasma total calcium levels are more commonly measured compared to ionized calcium levels; however, the superiority of one test over the other has been debated. If the total serum calcium level is used, it needs to be corrected based on the patient's albumin level. This correction is made by adding 0.8 mg/dL to the total serum calcium measurement for every 1 g/dL below the serum albumin concentration of 4 g/dL.

Indications for Treatment

The clinical presentation of primary hyperparathyroidism has changed from patients with symptomatic disease to those with only biochemical evidence of disease incidentally found on routine laboratory examination. Asymptomatic PHT has spurred investigation into the natural history of this disease and indications for treatment. It is accepted that surgery is indicated in patients who present with symptomatic PHPT such as nephrolithiasis,

nephrocalcinosis, renal dysfunction, osteopenia with fractures, osteitis fibrosa cystica, and altered neurologic function with obtundation, delirium, or coma [4]. However, the management of patients with asymptomatic PHPT has been controversial. The National Institutes of Health organized a consensus development conference in 1990 that made recommendations for the management of patients with asymptomatic PHPT. These recommendations were subsequently updated in the 2002 National Institutes of Health Work-shop on Asymptomatic Primary Hyperparathyroidism [3, 30, 34]. The summary of these recommendations for the surgical management of patients with PHPT is presented in table 1. Under these guidelines, the indications for surgery include a serum calcium concentration of 1.0 mg/dL above the upper limit of normal, urinary calcium excretion of >400 mg/24h, a reduction in the creatinine clearance of more than 30%, a bone mineral density with a t score below 2.5 at any site, age younger than 50 year or those who cannot participate in appropriate follow-up [35]. Some authorities, however, recommend a more liberal guidelines in the management of these patients due the inability to predict whether the complications or progression of disease will develop in a specific patient [36]. The 2002 guidelines for monitoring patients with asymptomatic PHPT who do not undergo parathyroid surgery are measuring serum calcium level every 6 months, annual measurement of serum creatinine concentration and annual bone density measurement at all 3 sites (the lumbar spine, the hip and the distal third of the radius) [4].

Localizing Studies

The treatment of hyperparathyroidism involves the removal of abnormally enlarged parathyroid gland(s) with the goal of rendering the patient with normal PTH levels and eucalcemic. Four-gland parathyroid exploration has been the gold standard for parathyroid surgery until recently. John Doppman made a classic statement in 1986 that “the only localization study indicated in a patient with untreated primary hyperparathyroidism is the localization of an experienced parathyroid surgeon.”[37] However, minimally invasive and focused parathyroidectomy has become a widely accepted approach for the treatment of primary hyperparathyroidism. The major limitation of this approach is the imperfection of the preoperative localization techniques. A summary of various localization techniques is provided in table 2. Through the use of combined preoperative and intraoperative techniques, this approach has achieved cure rates of greater than 95% with low morbidity [38]. The success of the localization studies also depends upon the experience of the institution. Invasive localizing studies, such as angiography and selective venous sampling, are rarely used now because of the high success rate of noninvasive approaches. However, if preoperative non-invasive studies are inconclusive intraoperative or preoperative office based ultrasound guided jugular venous sampling can be helpful in lateralizing the most hyperfunctioning parathyroid gland(s) [39].

Ultrasound

Among anatomic imaging modalities, ultrasound is the most frequently used imaging modality with the lowest cost, and has the advantage of not using ionizing radiation in this setting. It is, however, highly user-dependant and does not enable retromanubrial or mediastinal visualization. Normal parathyroid glands are rarely visualized by ultrasonography, because of their small size and insufficient acoustic difference compared to adjacent thyroid tissue. However, parathyroid adenomas, hyperplasia, and carcinomas exhibit a relatively hypoechogenic pattern, due to their compact cellularity relative to thyroid tissue [40]. Parathyroid adenomas are usually well-circumscribed ovoid, longitudinal in shape and tend to be solid and homogeneously hypoechoic relative to echogenic thyroid tissue (Figure 1) [12, 41, 42]. Overall, the ability to detect a parathyroid adenoma is a function of its size and the pathology of the adjacent thyroid tissue [43]. Ultrasound (US) is

inexpensive and highly sensitive in experienced hands. The sensitivity of US for detecting enlarged parathyroid glands ranges from 70% to 100% [34, 38-40]. False positive or negative sonographic diagnosis may be due to thyroid nodules, prominent blood vessels, cervical lymph nodes, esophagus and longus colli muscle [41]. The smaller the adenoma, the more difficult it is to localize radiographically, and in the setting of multinodular goiter, parathyroid adenomas may be overlooked due to poor sonographic penetration. In the presence of thyroid gland abnormalities, the sensitivity of US to identify abnormal parathyroid glands decreases ranging from 47% to 84% [43-46]. The identified concurrent thyroid disease should be addressed preoperatively by fine needle aspiration or intraoperatively in these patients. Ectopically located glands particularly intra thyroidal or retroesophageal glands make the sonographic detection of the parathyroid glands more challenging and difficult. The US sensitivity also decreases in patients with persistent or recurrent hyperparathyroidism. This sensitivity is reported between 36% and 63% [47, 48]. The sensitivity of surgeon performed US is reported to be comparable to radiologist performed US in localizing parathyroid adenomas and this may be advantageous for experienced endocrine surgeons [49]. An advantage of this technique is that it provides dynamic imaging in the hands of the surgeon who has an intimate knowledge of the cervical anatomy. If the US findings are inconclusive, additional localizing techniques such as Tc-sestamibi scan should be used.

Sestamibi Scan

The thallium technetium scintigraphy was popular in the late 1980s for the diagnosis of cervical and mediastinal parathyroid adenomas [50]. However, sestamibi (Technetium-99m-methoxyisobutyl isonitrile) which was used for evaluation of myocardial perfusion, was noted to have selective affinity for abnormal parathyroid glands [51]. Sestamibi has become the radiopharmaceutical of choice for parathyroid nuclear localization studies. Two different techniques are used to differentiate sestamibi uptake by abnormal parathyroid glands from uptake by the thyroid gland. The first, uses sestamibi as a substitute to Tl-201 in a dual radionuclide approach with subtraction imaging (with either I-123 or Tc-99m pertechnetate) and the second approach uses sestamibi alone (single radiotracer) with early and delayed imaging (dual phase study). Subtraction imaging is performed with the coadministration of a thyroid imaging agent, such as ^{123}I - or $^{99\text{m}}\text{Tc}$ pertechnetate and sestamibi as a thyroid-parathyroid agent [52]. The thyroid images generated are then digitally subtracted from the sestamibi image and the residual signal after subtraction of the thyroid image is indicative of parathyroid uptake [53, 54]. Various protocols have been described based on the type of the thyroid imaging tracer used and the sequence of tracer administration. $^{123}\text{I}/^{99\text{m}}\text{Tc}$ -sestamibi and $^{99\text{m}}\text{TcO}_4^-/^{99\text{m}}\text{Tc}$ -sestamibi, dual tracer subtraction techniques have been used in parathyroid imaging with limitations such as long imaging time or high thyroid counts [55, 56]. The use of a pinhole collimator in the neck can increase the imaging resolution; however, it will increase the image acquisition time. Regional perfusion, gland size and functional activity, cell cycle phase, and prevalence of mitochondria-rich cells are some of the factors affecting the diagnostic accuracy of $^{99\text{m}}\text{Tc}$ -sestamibi imaging of parathyroid glands [57, 58].

In the dual phase technique, the net retention of sestamibi in thyroid decreases significantly more rapidly than in parathyroid adenoma over time (1-3 hours post injection). This technique relies on the differential washout of sestamibi from thyroid tissue than from abnormal parathyroid glands [59, 60]. Images are obtained after the administration of sestamibi and then again approximately 2 hours later (Figure 2). The greater number of mitochondria in parathyroid tissue sequester sestamibi intracellularly. The patient's neck immobilization is an essential step in double-tracer subtraction scintigraphy that is not required for dual phase imaging. Technical simplicity of dual phase MIBI scintigraphy is a major advantage of this technique. Conversely, a major limitation of dual phase MIBI scan

in detecting parathyroid gland pathology is the association of HPT with thyroid nodular disease. In a study of 39 patients undergoing dual phase MIBI scintigraphy, 41% of the patients with positive MIBI scan had thyroid carcinoma [61]. Thyroid pathology, such as hyperplastic nodules, chronic thyroiditis, hurthle cell lesions and adenomas can have increased sestamibi uptake and retention, resulting in a false positive study, and high washout from the parathyroid tissue can result in false-negative findings [62]. Correlation with anatomic imaging and the use of subtraction techniques are important in these cases. Regardless of which technique is used, sestamibi scanning as a single modality for identifying adenomas has a reported sensitivity of 54%–100%, with most series in the 80% or 90% range [63-66]. Many studies looked at the sensitivity of US compared to sestamibi scanning have showed no significant difference in the sensitivity of the two techniques in detecting abnormal parathyroid glands [65]. In one recent study of 516 patients undergoing surgery for PHPT, surgeon performed US accurately localized adenomas in 87% of patients, and MIBI correctly identified their locations in 76% ($p < 0.001$) [67]. In patients who underwent US first, MIBI provided no additional information in 92%. The authors concluded that in experienced hands, US is more accurate than MIBI for predicting the location of abnormal parathyroid glands in PHPT patients.

Addition of single photon emission computed tomography (SPECT) is shown to increase the sensitivity and specificity of parathyroid scintigraphy allowing for better localization of the enlarged glands. The superposition of the two radio markers results in more accurate location of the abnormal gland [66, 68, 69]. In one study, addition of SPECT significantly improved the sensitivity for the detection of parathyroid adenomas to 79% from 54% for MIBI alone. In principle, SPECT offers the advantage of better discrimination of focal ^{99m}Tc -sestamibi retention in thyroid nodules and the parathyroid tissue. This technique is particularly useful for the localization of ectopic parathyroid adenomas such as mediastinal glands. Additionally, the sensitivity of this technique is lower for hyperplastic parathyroid glands compared to parathyroid adenomas. The sensitivity of identifying hyperplastic parathyroid glands using these techniques is reported from 25% to 58% compared to 54% to 98% for parathyroid adenomas [69-71]. When localizing studies are undertaken, frequently a sestamibi scan is used in conjunction with some type of anatomic imaging, either ultrasound, CT, or MRI. Several studies have reported the utilization of SPECT/CT for localization of parathyroid adenomas and hyperplasia in patients with previously untreated primary hyperparathyroidism (Figure 3). The results have been variable, with some series demonstrating improved sensitivity and positive predictive value resulting in a change in therapeutic management and others reporting no additional clinical value when evaluating patients with previously untreated PHPT [72-74]. In some reports SPECT/CT is shown to be valuable in locating ectopic parathyroid glands [73].

Computed Tomography

Computed tomography (CT) scanning can provide valuable and complimentary localizing information for the identification of abnormal parathyroid glands. This technique relies on the vascularity of the parathyroid glands and their relative enhancement with contrast compared to the surrounding structures (Figure 4). CT has reported sensitivity of 40% to 86% depending on the size of the lesion with the accuracy that is dependent on the technique and the experience of the radiologist [75-77]. In a study of 63 patients with negative sestamibi who underwent thin cut CT scanning, a sensitivity of 66% and specificity of 89% for identifying the exact location of diseased gland was observed. This allowed for 66% of the patients to undergo focused parathyroid exploration [78]. Parathyroid glands can be difficult to identify by CT at the area of the sternal notch and mediastinum due to streak artifact or being mistaken with lymph nodes. CT is also not particularly useful in identifying the parathyroid glands in patients who are not able to receive IV contrast. Some authors

advocate for the use of computed tomography in patients with inconclusive or discordant ultrasound and MIBI results [75]. Additionally, CT scanning may be useful in identifying ectopic parathyroid glands. In one study, CT had a sensitivity of 40% and specificity of 88% in identifying ectopic parathyroid glands [76]. CT scanning appears to be effective in localizing parathyroid disease as an adjunct to conventional first line imaging techniques.

In 2006, Rodgers et al. published their report of a new CT protocol for localizing parathyroid glands in patients with PHPT. They called this 4D-computed tomography (4D-CT) because of addition of changes in the perfusion of contrast over time to the three dimensional anatomic CT images [79]. This allowed for addition of functional information to the anatomic images due to the rapid uptake and washout of the contrast from the hyper-functioning gland to the anatomic data. They demonstrated an improved sensitivity of 88% for 4D-CT compared to sestamibi (65%) and ultrasonography (57%) for lateralizing the hyper-functioning gland and further allowed for improved localizing to the correct quadrant compared to the other two imaging modalities. More recently, Kutler et al. using a combination of 4D-CT/US technique reported a sensitivity of 94% and specificity of 96% for lateralizing the hyper-functioning parathyroid and a sensitivity of 82% for localizing the gland to the correct quadrant [80]. They reported a positive predictive value of 92% for a single gland and 75% for multi-gland disease for the combination of 4D-CT/US. This combination technique appears to be an excellent and cost effective preoperative localizing technique for hyper-functioning parathyroid glands.

Magnetic Resonance Imaging

Another anatomic imaging modality used for detecting abnormal parathyroid glands is magnetic resonance imaging (MRI). Parathyroid adenomas are isointense relative to the surrounding muscle and have low intensity on T₁ weighted images. They are generally hyper intense on T₂ weighted images; however, hyper-functioning parathyroid glands show intense contrast enhancement on T₁ weighted images (Figure 5) [81]. This method is preferred by some over CT scanning due to lack of ionizing radiation. The sensitivity of MRI in detecting abnormal parathyroid glands is reported from 69% to 88% with a false positive rate of 1.6% to 10% [82-84]. Factors resulting in false positive disease are concomitant thyroid disease and enlarged cervical lymph nodes that may mimic parathyroid adenomas. In a study comparing the sensitivity of MRI to MIBI and US in patients with recurrent or persistent hyperparathyroidism, the overall sensitivity of the three modalities were 88%, 80% and 58%, respectively, with the accuracy of 84%, 80% and 44% respectively. This accuracy increased to 92% when MIBI and MRI results were combined [83]. MRI is less sensitive and specific in identifying hyperplastic glands compared to parathyroid adenomas [85]

Intraoperative Parathyroid Hormone Assay

The half-life of PTH in the circulation is approximately 2-4 min. Generally, more than 50% drop in the PTH level taken in the operating room after the removal of the suspected gland indicates that the source of the hyperparathyroidism is removed. The blood draw after removal of the suspected adenoma should occur 10 min after the specimen is excised [86, 87]. In a study comparing 421 patients who underwent intraoperative PTH (IOPTH) assay guided limited parathyroidectomy to 340 patients undergoing bilateral neck exploration, IOPTH guided limited parathyroidectomy was successful in 97% of the cases with 3% bilateral exploration for multiglandular disease [88]. Some authors strongly advocate the use of IOPTH in the management of PHPT and believe that it improves the cure rate of patients undergoing minimally invasive parathyroidectomy [89]. However, the benefit of intraoperative parathormone assay in the presence of concordant preoperative localization

studies may be marginal [90]. An analysis of 210 published series using intraoperative PTH calculated that a unilateral neck dissection was completed as intended in 94.5% of the cases. IOPTH levels resulted in conversion to a bilateral neck exploration in 5.5% of cases. Persistent hypercalcemia after all cases in which IOPTH was used was 1.3% [91]. However, some authors have reported excellent success rates as high as 97% in patients undergoing minimally invasive parathyroidectomy without IOPTH when preoperative imaging studies are concordant in identifying the abnormal glands [92, 93]. In one retrospective study, using decision tree and cost analysis model to examine IOPTH monitoring in localized PHPT, IOPTH marginally increased the cure rate in minimally invasive parathyroidectomy while incurring approximately 4% additional cost [94].

Additionally, intraoperative or preoperative differential selective internal jugular venous sampling and measurement of the PTH level has been reported with good success in lateralizing the hyperfunctioning gland(s). In a study of 21 patients with unequivocal preoperative surgeon performed US, office based differential jugular venous sampling was successful in 81% of the cases to lateralize the side of the abnormal gland [39].

Treatment Options

There is no convincing data to support the long term efficacy of medical therapy or observation in the management of patients with PHPT. The definitive treatment of PHPT is the surgical removal of the hyperfunctioning tissue. Before the widespread use of localization studies and intraoperative rapid PTH assays, the treatment of PHPT was bilateral neck exploration with the goal of locating and visually evaluating all 4 parathyroid glands. This technique yields excellent results and became the gold standard for the treatment of PHPT [95-97]. The success of four gland exploration in identifying the hyperfunctioning gland(s) and treating the patient with PHPT approaches 95% [18, 95, 98]. Bilateral neck exploration generally involves making an incision similar to the one used for thyroid surgery. Both lobes of the thyroid gland are mobilized, both recurrent laryngeal nerves are identified, and the neck is explored to identify 4 parathyroid glands. Direct visualization is often sufficient for the identification of the abnormal gland or glands based on size and shape. Frozen section sampling can also be helpful for comparing an abnormal gland with a normal parathyroid or non-parathyroid tissue.

It is known that 80% to 90% of patients with PHPT have a solitary parathyroid adenoma, and in these patients only one gland requires excision for cure [98, 99]. In these patients, a focused surgical approach will result in reduced risk of post-operative hypocalcemia and vocal cord injury [100-102]. For the minimally invasive and focused surgical approaches to be successful, preoperative localization techniques are essential to guide the surgical planning. If a sestamibi scan, in combination with anatomic imaging such as an ultrasound or CT, indicates a single adenoma, then it is possible to focus the surgical attention to the area of the diseased gland. In a retrospective review of 656 consecutive parathyroid explorations, the success of minimally invasive parathyroidectomy (MIP) was 98% with a low complication rate of 1.2% compared to 3.0% for the standard bilateral exploration technique [103]. MIP was associated with decreased hospital length of stay and costs. Intraoperative PTH assay is usually used to confirm the preoperative imaging findings. This focused approach can be achieved via unilateral exploration or a single gland exploration. A unilateral neck exploration involves making a smaller 3-5 cm incision and exploring 1 side of the neck with the goal of identifying both parathyroid glands and the recurrent laryngeal nerve. A focused single-gland exploration involves making an incision 2-4 cm long. IOPTH helps to increase the certainty that the gland or glands responsible for the PHPT are addressed at the time of the focused surgery. In focused parathyroid surgery, some surgeons directly look for the abnormal gland without identifying the recurrent laryngeal nerve.

However, in case of 4-gland hyperplasia, bilateral neck exploration for a successful outcome and identification of all glands is required [104]. Either 3.5 parathyroid glands are excised, or all 4 glands are excised with re-implantation of parathyroid tissue in the sternocleidomastoid muscle or in the forearm. In the case that the intraoperative PTH level does not drop adequately, 50% drop or normalization of PTH level, a bilateral four gland exploration is required and the surgeon and patient must be prepared for such scenario.

With the trend toward increasingly minimally invasive techniques, endoscopic parathyroidectomy has been practiced in some centers. This technique is referred by some authors as minimally invasive video assisted parathyroidectomy. Candidates for this technique usually have localizing studies that strongly suggest a single abnormal gland with favorable anatomy. Patients with anatomic features such as enlarged thyroid gland, short neck or obesity are not ideal candidates for this approach [105]. Endoscopic techniques using gas insufflation are uncommon in the United States. The advantage of this technique is that it allows incisions to be placed farther from the gland, such as below the clavicle or in the axilla, in an effort to improve cosmesis [106, 107]. However, the disadvantage is that subcutaneous crepitus and dissection of gas into surrounding tissues can occur. A more commonly used endoscopic technique involves making a 1.5- to 2-cm lateral cervical incision and placing an endoscopic instrument through this incision or a centrally placed incision that allows bilateral exploration. Through this incision, the endoscope and the instruments are placed allowing for magnification, retraction and dissection of the tissues. These techniques are used to improve the cosmetic outcome of the surgery; however, in those with skin crease in the neck, the cosmetic difference with minimally invasive parathyroidectomy is minimal.

Radioguided parathyroid surgery has been described using the physiological and functional aspect of increased sestamibi in a hyperfunctioning parathyroid gland. Patients are given ^{99m}Tc -sestamibi, and imaging is performed on the day of surgery. The success of radioguided surgery is dependent on the differential kinetics of ^{99m}Tc -sestamibi in thyroid and parathyroid glands. ^{99m}Tc -Sestamibi washes out more rapidly from the thyroid than from the parathyroid glands. Various protocols have been developed to optimize the parathyroid to thyroid count allowing for better intraoperative localization of the parathyroid glands [108, 109]. A mark is made on the skin by the nuclear medicine physician, communicating to the surgeon the evidence of an adenoma. Intraoperatively, a gamma probe is used in the surgical wound to identify the hyperfunctioning glands and to help guide the dissection [110]. Usually a small 2- to 3-cm incision is used in this single-gland exploration technique. Murphy and Norman in their study of 345 patients who underwent radio guided parathyroidectomy concluded that 20% of the background radioactivity in a patient with positive sestamibi scan reveals a solitary parathyroid adenoma [110]. The authors suggested that this could eliminate the need for IOPTH assay and frozen section analysis. However, the usefulness of this technique in the presence of a localized preoperative sestamibi scan has been debated [111].

Conclusion

The treatment of parathyroid disease is primarily surgical. However, minimally invasive parathyroidectomy would not be successful without accurate preoperative localization of the abnormal gland. This requires skilled radiologists at performing sestamibi scanning, ultrasonography and other imaging modalities to guide the surgeon in localizing the abnormal gland(s). The ability to perform rapid IOPTH can also improve the cure rate of this technique and confirming the preoperative findings.

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Figure 1.
Hypoechoic left lower pole (A) and behind the left lower pole (B) parathyroid adenomas identified by ultrasound

Figure 2. Image after administration of sestamibi (2-h) delay demonstrates left inferior parathyroid adenoma.

Figure 3.
SPECT/CT demonstrating a right side parathyroid adenoma

Figure 4.
Computed tomography demonstrating a left sided parathyroid adenoma

Figure 5.
MRI demonstrating a left parathyroid adenoma

Table 1

Surgical indications in patients with primary hyperparathyroidism. (Adopted from the 2002 National Institutes of Health Work- shop)

1. Significant bone, renal, gastrointestinal, or neuromuscular symptoms typical of primary hyperparathyroidism	
<i>In asymptomatic patients</i>	
2. Serum calcium	Elevation by 1 mg/dl or more above the normal range (i.e., 11.5 mg/dl in most laboratories)
3. 24-hour urine calcium excretion	Marked elevation (e.g., >400 mg)
4. Creatinine clearance	Decreased levels (e.g., reduced by 30% compared with age-matched normal persons)
5. Bone density	reduction in bone density of more than 2.5 standard deviations below peak bone mass at any measured site (hip, lumbar spine, wrist; i.e., "T score" approximately <2.5 at any of these sites)
7. Age	younger than 50 years

Table 2

parathyroid localization Studies

Noninvasive	Invasive
High-resolution US	Selective venous sampling
Tc 99m Sestamibi scan	Angiogram
CT scan	Digital subtraction
MRI	US guided FNA
SPECT-CT	US guided Jugular Venous sampling
4D CT	