REVIEW ARTICLE

Reoperative Surgery for Recurrent or Persistent Primary Hyperparathyroidism

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Introduction

Primary Hyperparathyroidism (PHPT) is the third most common endocrine disorder and the most common cause of hypercalcemia in the outpatient setting (1). It is defined as hypercalcemia secondary to overproduction of PTH by one or more parathyroid glands.

Primary hyperparathyroidism (PHPT) has been recognized as a disease process since the 1920s when it was discovered in both the United States and Europe (2). The first parathyroid surgery was performed in 1925 by Felix Mandl in Vienna, Austria who showed that by removing the affected gland, the patient had resolution of severe symptoms associated with the disease (3). Since then, the recognition and treatment of PHPT have evolved because of improved laboratory testing, accurate preoperative localization and less invasive surgical procedures.

The prevalence of PHPT is in the range of 0.1-0.4 percent, and the incidence increases with age reaching a peak between 50-60 years of age (1,4). PHPT has a higher frequency in women and in patients who have a history of neck irradiation (5). We recently showed that there is a racial disparity related to the presentation of this disease. We found that African Americans present with more advanced signs of primary hyperparathyroidism than non-African Americans (6). Once a diagnosis is made, preoperative localization of the involved gland or glands aids in the choice of operation.

Most cases are sporadic; however, approximately 5 % of cases are familial. Patients can present with single or double adenomas, multigland disease (MGD) or rarely, parathyroid cancer. Several studies have shown that the overwhelming majority of patients have a single adenoma (80-85%). MGD occurs less frequently (10-15%) and double adenomas are even more rare (4-5%). Parathyroid cancer is diagnosed in less than 1% of patients with HPT (7).

The diagnosis of PHPT is usually made biochemically with an elevated serum calcium and elevated PTH (1).Some patients will present with normocalcemia which is within the continuum of the disease. Patients can also have PTH values within the reference range which reflects an inappropriate response to hypercalcemia. Measurement of a 24-h urine calcium level can also be helpful, as a value of less than 30 mg is suggestive of familial hypocalciuric hypercalcemia (FHH), a mild hypercalcemic condition that rarely requires surgical intervention. Vitamin D levels should be checked initially in all patients with a diagnosis of PHPT because the presence of vitamin D deficiency can affect the interpretation of the PTH assay resulting in elevated PTH levels (8).We recently showed that patients with vitamin D deficiency present with more advanced indices associated with PHPT. We also showed that Parathyroid sestamibi scanning was more likely to show positive results for this subset of patients who may then benefit from sestamibi scan-directed surgical intervention (9).

Persistent and Recurrent Primary Hyperparathyroidism

Cure of PHPT is most readily achieved during initial neck exploration. Unfortunately, a subset of patients will require re-exploration for persistent or recurrent disease. Neck re-exploration is technically difficult due to distortion of neck anatomy by fibrosis and frequently obliterated normal tissue planes.

Definitions

1-Recurrent disease is defined as redevelopment of PHPT more than six months after initial curative surgery. Between 1% and 6% of PHPT patients will experience persistent disease or will develop a recurrence after initial resection (10). Accordingly, all patients require confirmation of cure following initial exploration (11).

2-Persistent disease is defined as persistent postoperative elevation of intact parathyroid hormone (iPTH), in association of rising serum calcium levels. Initial postoperative serum iPTH levels are commonly elevated in the context of low calcium following curative resection. This is usually a postoperative normal physiologic response due to relative hypocalcemia and is usually self-limited (12).

Accordingly, reoperative surgery carries an increased risk of injury to recurrent laryngeal nerve(s) as well as to normal residual parathyroid tissue. Pathologic hyperfunctioning parathyroid tissue is also more frequently ectopic in the re-operative setting and can thus be difficult to localize. Nonetheless, excision of culprit hyperfunctioning parathyroid tissue continues to be the standard of care for these challenging scenarios.

Indications for Reoperative Parathyroid Surgery

Surgical intervention for PHPT in patients with no previous surgical intervention affords a cure rate greater than 95%. However, there are no data specifically addressing the efficacy of surgical versus nonsurgical interventions for recurrent or persistent asymptomatic disease, and it is therefore reasonable to consider similar guidelines when assessing asymptomatic patients with persistent or recurrent disease for surgical referral.

Indications for surgery include patients with overt clinical signs or symptoms such as kidney stones, decreased bone density, prior fracture or brown tumors (13). For patients who have a biochemical diagnosis but are asymptomatic, the NIH has developed a set of guidelines which were modified in 2008 (Table 1). They include a serum calcium level 1.0mg/dl or greater above the upper limit of normal, creatinine clearance less than 60 ml/minute, BMD T-score or Z-score less than -2.5 at any site or prior fracture fragility and age less than 50. A 24 hour urine calcium level is no longer indicated per the new guidelines (13). Patients who have vague symptoms and a biochemical diagnosis should also be strongly considered for surgery. Several studies report overall improvement especially in neurocognitive symptoms and better quality of life for these patients after parathyroidectomy (4,14,15).

Preoperative evaluation

A careful preoperative assessment is required to optimize outcomes for these challenging patients. A thorough history and physical exam, including laryngoscopic vocal cord evaluation and biochemical verification of PHPT should be considered in preoperative evaluation. The risk of increased morbidity associated with re-exploration should be discussed with the patient. Asymptomatic patients with persistent or recurrent disease referred for surgical evaluation that have borderline elevation of iPTH and calcium levels may be followed clinically, with operative intervention offered for disease progression.

Table 1
NIH guidelines (2008) for surgical treatment of asymptomatic PHPT

- Serum Ca > 1.0 mg/dL above upper limit of normal.
- Creatinine clearance <30% of age-matched normal subjects.
- Diminished bone density (T score <-2.5) and /or fragility fracture.
- Age <50 years old.
- Difficult periodic follow-up.

Ectopic parathyroid tissue and supernumerary parathyroid glands are more common and present in as many as 53% of re-operative cases (16). Preoperative localization imaging will assist the surgeon in minimizing the extent and morbidity of re-exploration.

Preoperative Imaging

Preoperative localization of abnormal parathyroid glands has become very important in the era of minimally invasive parathyroid (MIP) surgery. The two most common imaging modalities are ultrasonography and ^{99m}Tc-sestamibi scintigraphy. Using these two modalities together increases the accuracy of localizing the suspect gland. CT and MRI are less employed but are useful in patients with failed parathyroidectomy, recurrent or persistent HPT in order to identify ectopic glands (Table 2) (17). Initial preoperative imaging should be noninvasive and relatively inexpensive, reserving invasive and costly techniques for cases initial non-localizing imaging modalities.

Ultrasound	Sestamibi	CT	MRI	PET
60-92%	78-100%	36-100%	51-100%	70-74%

Table 2: Positive predictive values for various preoperative diagnostic modalities

The most commonly employed studies are ultrasound and sestamibi scans, both of which are inexpensive and readily available. The sensitivity of sestamibi scans can be dramatically enhanced by co-imaging with single photon emission computed tomography (SPECT) scanning, which allows three-dimensional localization of parathyroid lesions [18].

1- Parathyroid Sestamibi scans:

^{99m}Tc-sestamibi is taken up by both parathyroid and thyroid tissue making it a logical choice for preoperative localization in patients with HPT. Adenomatous and hyperplastic parathyroids have more avid and more prolonged uptake than the thyroid tissue [17]. Therefore, after injection of the radiotracer, one set of images is taken within 15 minutes and then a delayed set is taken at two hours. Asymmetry of uptake can be noted on early images, but usually, the delayed images are necessary to locate the focus of radiotracer which characterizes hyperfunctioning parathyroid (Figure 1).

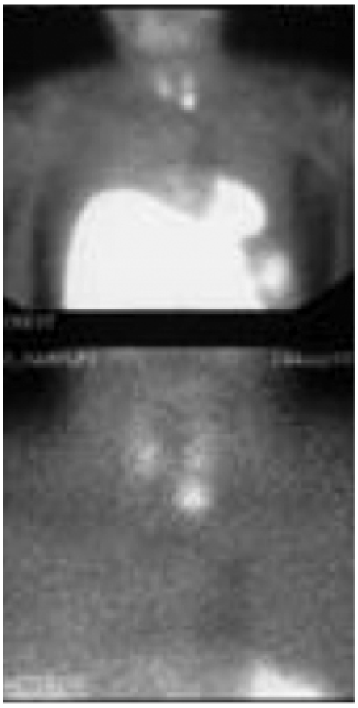

Figure 1: Sestamibi scan demonstrating radiotracer uptake in the left inferior thyroid bed for a patient with PHPT.

2- SPECT scans:

SPECT, single photon emission computerized tomography, can help differentiate parathyroid tissue from thyroid tissue increasing the sensitivity of scintigraphy (Figure 2). For solitary adenomas, there is a sensitivity of 87 percent when using SPECT. Its sensitivity decreases with double adenomas (30%) and MGD (44%) [17]. A hybrid of SPECT and CT used for the early images has also been shown to enhance the accuracy of localization when combined with various delayed imaging methods particularly dual phase imaging which is better than single phase imaging [19].

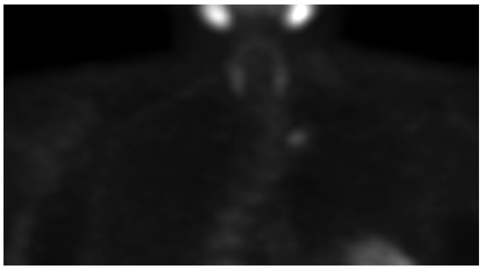

Figure 2: SPECT scan demonstrating aberrant radiotracer uptake in the left superior anterior mediastinum of a persistent primary hyperparathyroid patient. Note the physiologic uptake of radiotracer by normal salivary glands.

3-**High resolution ultrasound** is a useful modality to locate enlarged parathyroid glands in the neck. On ultrasound, a parathyroid adenoma is hypoechoic, homogenous and solid with a bean shaped or oval appearance (Figure 3). There is usually a small branch from the inferior thyroid artery which enters the gland at one of its poles. One of the benefits of cervical ultrasound is the ability to study the thyroid gland concurrently for any abnormalities. Eighteen percent of patients with PHPT have synchronous thyroid disease with an overall mali[illegible] [20].

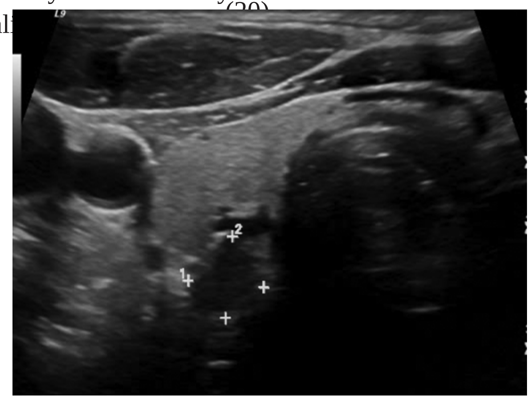

Figure 3: Ultrasound demonstration of a parathyroid adenoma

Ultrasound is also beneficial because it is inexpensive, it does not use ionizing radiation, and it has a sensitivity in the range of 72-85 percent [17,21]. One downside of ultrasonography is the difficulty in finding glands located in the mediastinum, the retroesophageal space and other ectopic location.

The combination of ultrasound and ^{99m}TC-sestamibi scintigraphy to preoperatively localize parathyroid adenomas increases the sensitivity to 95 % because each modality contributes different data to help determine the gland location [17].Ultrasonography is more specific for anatomic location of the gland in relation to the thyroid while scintigraphy is better at finding ectopic glands especially in the mediastinum [17]. For double adenomas and MGD, the sensitivity continues to be lower even when these modalities are combined.

4-CT of soft tissues of the neck:

For patients with persistent disease, CT with thin cuts from the skull base through the chest can identify contrast enhanced parathyroid tissue with a sensitivity ranging from 46-87% [17]. CT is particularly useful in patients who have altered anatomy or a failed parathyroidectomy (Figure 4).

5- MRIs:

MRIs which are rarely done can also identify abnormal parathyroid tissue and are utilized in patients with recurrent or persistent disease [17].

Computed tomography (CT) scanning and magnetic resonance imaging (MRI) can be useful in localizing ectopic mediastinal lesion that would otherwise be undetectable by ultrasound. Positron emission tomography (PET), which is often combined with CT scanning, is mo nal inte ing peri

Figure 4: Contrast computed tomography (CT) scan demonstrating a parathyroid adenoma within the thymus, in the anterior mediastinum, of a remedial 1^{ry} HPT patient.

Additional Preoperative testing

1- Fine needle Aspiration (FNA) of parathyoid adenoma:

Assessment of PTH levels in parathyroid lesions using fine needle aspirates (FNA) under ultrasound guidance can be also employed with reported 87% sensitivity and 74% specificity [22].

2- Selective Venous Sampling:

Selective arteriography and venous sampling for PTH is an invasive imaging modality that can be employed with reported 84% sensitivity and 88% specificity. This technique is expensive, requires considerable technical expertise, and can be associated with groin hematomas and vascular injury. Thus, it should be reserved for cases in which other imaging studies fail to localize the culprit for the disease persistence or recurrence.

In Summary, recent advances in preoperative localization have lead to significant improvements in outcomes after reoperative surgery. However, it is prudent to reassess the operative indications in patients with persistent negative localization studies to determine if they can be maintained without surgery.

Intraoperative adjuncts

1- Intraoperative PTH (IOPTH):

Intact PTH has a half-life of less than 5 minutes with the majority of its metabolism in the liver and the remainder in the kidney. Intact PTH assays detect 1-84 PTH as well as large c-terminal fragments which can alter PTH values. Bio-intact and whole PTH assays utilize an antibody that is specific for the complete molecule, 1-84 PTH, minimizing the possibility of amino acid fragments from affecting PTH values. These assays are second and third generation assays which have similar sensitivities in diagnosing PHPT [23,24]. Various second and third generation assays are available, and they use similar types of analyses with comparable turnaround times between 10 and 15 minutes [25,26].

IOPTH is used to determine the adequacy of resection of parathyroid tissue in order to prevent operative failures secondary to missed multigland disease (MGD) [27,28]. IOPTH levels predict postoperative calcium levels because of the dynamic change in hormone following resection of all hypersecreting glands.

Success of surgery is considered with a 50% or greater drop from the highest PTH level drawn to the PTH level measured 10 minutes after gland excision. Specifically, a pre-incision PTH level is drawn as well as a pre-excision level because of the possibility of gland manipulation with a further increase in PTH from the original baseline value [27]. IOPTH has an overall accuracy of 97%. Successful parathyroid surgery is determined by both postoperative calcium levels and calcium levels at 6 months that are within normal limits [27].

2- Intraoperative Recurrent Laryngeal Nerve(s) Monitoring:

The gold standard for prevention of RLN injury continues to be direct visualization and identification of the nerve [29]. Intraoperative nerve monitoring is used by many surgeons as an additional method for ensuring RLN continuity [30].

The nerve monitor should be used to document a complete circuit exists after the nerve has been identified; however, there is no evidence to show that it is beneficial in first-time parathyroid surgery where rates of RLN injury are typically less than 1% [31].

3-Gamma Probe:

Radio-guided surgery using ^{99m}Tc-sestamibi and a gamma probe intraoperatively is advocated by some surgeons [32,33]. A positive sestamibi scan is obtained preoperatively for localization. On the day of surgery the patient receives an injection of ^{99m}Tc-sestamibi approximately two hours before surgery. Prior to making an incision the gamma probe is used to mark the area of uptake potentially by the affected gland [31-33]. A small incision is made over this area, and the gland is removed. Background counts are done as well as a count on the excised gland. With a success rate ranging from 77-100% in the literature, this method is not widely used because many surgeons do not find it beneficial [31].

Operative techniques

Hyperfunctioning parathyroid tissue in reoperative PHPT can be usually resected via a cervical incision.

Medial versus Lateral approach:

Medial approach is the standard approach for exploration which attempts to utilize the operative planes explored during the patient's initial surgery. Lateral approach, dissecting the plane between the strap muscles and the sternocleidomastoid muscle, allows avoidance of scarred tissues from previous exploration and allows posterior access to the thyroid bed [34]. However, medial approach allows for bilateral cervical exploration.

During Surgery, care must be taken not to rupture the gland on extraction because of the risk of cell spillage and subsequent parathyromatosis.

Most mediastinal disease is accessible via a cervical approach since the culprit is either retroesophageal or intrathymic. However, median sternotomy, partial sternal split, or video-assisted thoracic approach may be required [35].

Non operative option

Alcohol Ablation

Ultrasound-guided ethanol ablation of culprit parathyroid tissue has been proposed, however, it has an very low cure rate relative to surgical re-exploration. Additionally, RLN injury has been reported. Thus, it should be reserved for cases in which surgery cannot be safely performed [36].

Postoperative Complications

Complications for all of these procedures include persistent hyperparathyroidism, recurrent laryngeal nerve (RLN) injury, and transient postoperative hypocalcemia [37]. Adjuncts used to minimize these complications include accurate preoperative localization as previously discussed, intraoperative nerve monitoring, frozen section and postoperative oral calcium supplementation [31].

Postoperative Care

Cure rates following surgical re-exploration are between 94% and 96% with low complication rates in cases performed by experienced surgeons [38]. However, these patients require careful postoperative care as they are at risk for RLN injury and postoperative hypocalcemia. Although no protocol exists for calcium supplementation following parathyroid surgery, most surgeons place their patients on some type of oral calcium regimen which can be weaned over the course of a few week [33,39,40]. If these patients are discharged without a calcium regimen, they often have complaints associated with hypocalcemia such as perioral and extremity numbness and tingling which usually stops after oral calcium is begun.

Re-operative surgery for patients with recurrent or persistent primary hyperparathyroidism remains a significant challenge. If again persistent or recurrent disease is biochemically confirmed, throrough assessment should be carefully performed. Additional new work-up will include a detailed history and physical examination, repeat laryngoscopic evaluation and preoperative localization studies. Given the increased risk of complications with each repeat cervical exploration, asymptomatic patients having borderline biochemical evidence may be considered for nonoperative management.

Nonetheless, surgical re-exploration will be required with progressive clinical disease.

In summary, despite the significant challenges associated with re-operative surgery for recurrent and persistent PHPT, excellent outcomes can be reproducibly achieved when proper pre-, intra-, and postoperative management is employed.

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