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ORIGINAL ARTICLE

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Surgical Aspects of Primary Hyperparathyroidism

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ABSTRACT

Parathyroidectomy (PTX) is the treatment of choice for symptomatic primary hyperparathyroidism (PHPT). It is also the treatment of choice in asymptomatic PHPT with evidence for target organ involvement. This review updates surgical aspects of PHPT and proposes the following definitions based on international expert consensus: selective PTX (and reasons for conversion to an extended procedure), bilateral neck exploration for non-localized or multigland disease, subtotal PTX, total PTX with immediate or delayed autotransplantation, and transcervical thymectomy and extended *en bloc* PTX for parathyroid carcinoma. The systematic literature reviews discussed covered (i) the use of intraoperative PTH (ioPTH) for localized single-gland disease and (ii) the management of low BMD after PTX. Updates based on prospective observational studies are presented concerning PTX for multigland disease and hereditary PHPT syndromes, histopathology, intraoperative adjuncts, localization techniques, perioperative management, "reoperative" surgery and volume/outcome data. Postoperative complications are few and uncommon (<3%) in centers performing over 40 PTXs per year. This review is the first global consensus about surgery in PHPT and reflects the current practice in leading endocrine surgery units worldwide. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: PTH/VITAMIN D; PARATHYROID-RELATED DISORDERS; THERAPEUTICS-OTHER

Introduction

The only cure for primary hyperparathyroidism (PHPT) is surgery. Since its first description in 1925 by Felix Mandl, parathyroidectomy (PTX) has evolved through two distinct periods—before and after the implementation of localizing techniques. A worldwide expert panel representing multiple disciplines relevant to PTX framed specific topics to address including definitions, preoperative localization, outcome, adverse events, and safety. The group sought to deliver evidence-based guidance when possible.

Methods

The approach to the guidelines was standardized. A group of experts was convened with attention to an equal balance of gender and practice location and representation. Surgeons, endocrinologists, pathologists, and radiologists were included and

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asked to write their parts according to the best available evidence. Conflicts-of-interest forms were completed and recorded. Rules were established whereby any member with a conflict would be allowed to participate in text draft but would not be eligible for discussion of the recommendations. There was no surgical industry funding. Zoom conference calls were organized with a regular cadence. Value was placed on avoiding over utilization of investigation and in avoidance of increased morbidity or mortality. Continuous consideration was placed on resource utilization and practical approaches to contemporary parathyroid management dilemmas. Decisions were made by group consensus. Two chairs collaboratively oversaw the process and co-led the writing. A systematic review was performed using PubMed and Embase. Inclusion criteria included publication dates from 1980–2020 in the English language with primary data focusing on subtopics deemed suitable by the expert panel. Excluded were abstracts, case reports, letters, or opinions not based on data. Meta-analysis and risk of bias quality assessments were not performed based on nature of the questions posed. Nongraded recommendations involved none of these structured approaches and are presented as descriptions of the practice of the expert panelists in managing patients with PHPT.

Results and Discussion

The following are definitions of the main surgical approaches to PTX according to the results of imaging techniques and the type of disease. Since PHPT is most often (80%–85%) due to a single adenoma, a targeted selective approach gained support when Russell and Tibblin pioneered the technique in the early 1980s.[1,2] It has become the standard procedure for single adenoma excision. Bilateral exploration is recommended for patients with negative localization or known or suspected multigland disease (MGD). Standardization of terms was deemed necessary.

Definitions and descriptions of different surgical approaches

There are no current standard definitions of the different types of PTX. Here we present a consensus in naming surgical procedures related to parathyroid gland surgery.

1. *Bilateral exploration*. Four-gland exploration with resection of macroscopically enlarged gland(s).
   (a) Performed for known or suspected MGD: hereditary PHPT, lithium therapy, sporadic MGD.
   (b) Most often performed when localizing tests are negative. Although most patients with negative localization have single-gland disease, the likelihood of MGD increases in this setting.[3,4]
2. *Unilateral exploration*. Image-guided exploration of one side of the neck with excision of the adenoma and identification of the ipsilateral normal gland to rule out four-gland hyperplasia. This approach is less frequently performed than either bilateral exploration or targeted operations. Some authors have proposed unilateral exploration for PHPT-MEN 1 as "staged surgery,"[5] but this is controversial since less than subtotal resection procedures carry a high rate of persistence/recurrence.[6]
3. *Selective, targeted, or focused PTX*. Image-guided unilateral approach to excise a single parathyroid adenoma without purposeful identification of the normal ipsilateral gland. May be performed via a central or lateral approach. Straight minimal dissection access is provided by the lateral approach, but careful placement of the minicervicotomy is crucial for an uneventful excision of the adenoma.The term "selective" is preferred because it emphasizes removal of a single gland and implies careful patient selection.[7] All direct approaches to selective PTX (lateral minicervicotomy, endoscopic, video-assisted) should be considered minimally invasive. Remote endoscopic approaches should not be considered minimally invasive since they imply instrument tunnelization and aggressive soft tissue dissection.
4. *Conversion*. Selective PTX can be converted to a wide unilateral field exposure or to a bilateral exploration when (i) intraoperative findings are not concordant with preoperative imaging; (ii) technical difficulties arise (bleeding, megadenomas, goiter, recurrent nerve exposure); (iii) the intraoperative PTH level fails to decrease appropriately[8]; (iv) there exists a need for unplanned thyroidectomy; (v) surgeon's judgments based on findings at the initially explored side; or (vi) there is a suspicion of parathyroid carcinoma.[9,10]

For a patient with known or suspected MGD, bilateral neck exploration is the best surgical approach to perform in one of the following ways:

- *Subtotal PTX*. Currently, the gold standard for hereditary PHPT and, possibly, for lithium-associated parathyroid hyperplasia.[11-14]It consists of the excision of three glands and, if necessary, part of the fourth, leaving either a normal gland or a 40- to 50-mg remnant of viable tissue marked with a nonabsorbable suture or radiopaque clip to facilitate identification should reoperation be required. Concomitant transcervical thymectomy is recommended to resect supernumerary glands or additional intrathymic nests of parathyroid tissue (see following discussion).
- *Total PTX with immediate autotransplantation*. Once a procedure applied to PHPT-MEN1 and in preventive total thyroidectomy for MEN2A, total PTX is currently rarely performed, even by groups pioneering the procedure,[15] due to its high rate of permanent hypoparathyroidism. Immediate autotransplantation may have a select role in those who undergo reoperative PTX. Classically, the brachioradialis is the muscle site due to its proximity to the antecubital veins. Thus, venous blood draining of the site can be compared to the contralateral site to assess the functioning status of the autotransplanted tissue over time.[6,16]
- *Total PTX with delayed autotransplantation of cryopreserved tissue*. Initally suggested as an alternative approach to subtotal PTX for the management of PHPT-MEN 1,[17] this procedure is being abandoned due to poor long-term results[6] Total PTX, with either immediate or delayed autotransplantation, still has a role in reoperative surgery.[18] Prolonged cryopreservation reduces the likelihood of the autograft becoming functional.[19]
- *Transcervical thymectomy*. Performed by blunt dissection and pull-up of thyrothymic ligaments[20] aiming to (i) resect a localized fallen (Type F in nomenclature) parathyroid adenoma,[21] (ii) explore an ectopic position when conventional neck exploration is negative, or (iii) excise all residual parathyroid tissue after subtotal PTX for MGD to decrease recurrence rates in PHPT-MEN1.[11,22,23] It also theoretically lessens the risk of thymic neuroendocrine tumor development, especially in MEN1

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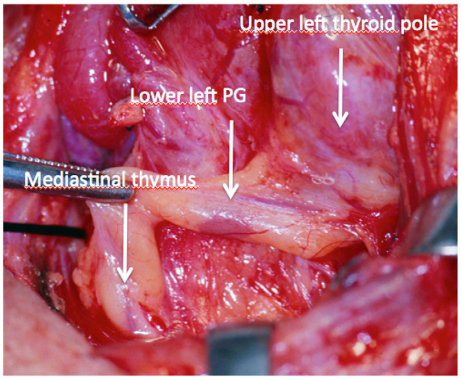

Fig. 1. Ectopic upper left thyroid pole insertion of thymus containing a normal intrathymic inferior parathyroid gland (courtesy of AS-S).

men. Normally, the thymus hangs from the inferior pole of the thyroid, but it may be undescended or attached to the upper pole of the thyroid (Fig. 1).

Extended (en bloc) PTX. Parathyroid carcinoma is a rare (<1%) cause of PHPT. The best chance for cure relies on the appropriate recognition by the surgeon at the time of PTX (adhesions, hardness, infiltration of surrounding tissues) performing an en bloc resection, including the ipsilateral thyroid lobe and tissue and, if necessary, the recurrent laryngeal nerve to obtain negative margins. Suspicious lymph nodes should be removed from the central compartment. Prophylactic lateral neck dissection is not necessary.[24]

Pathology of PHPT

Pathological variants causing hyperparathyroidism: Adenoma

About 80% of patients with PHPT have a sporadic single-gland adenoma, which by definition is a hypercellular gland over 80 mg (twice the normal weight). Larger glands up to 50 g have been reported. Adenomas less than 200 mg have been associated with a higher recurrence rate (6% versus 2%).[25]

Various histological types of adenoma are recognized, discussed in what follows.

Chief cell adenoma

The most common adenoma is composed of chief cells, followed by lesions with a predominace of chief cells and admixed oncocytes and clear cells (mixed histology). Although most adenomas are clonal proliferations, many of these lesions are multiclonal. The larger the adenoma, the less likely it is to have a rim of normal parathyroid tissue present. This finding is helpful in defining the lesion as an adenoma, however.[26]

Oncocytic adenomas

These can be seen in many endocrine organs and are believed to be either a less well-functioning cell or a degenerative phenomenon. On occasion an entire adenoma will be composed of oncocytes. Many of these adenomas are large but have lower PTH synthetic or secretory capacity with modest elevations of calcium and parathyroid hormone.[27]

Lipoadenoma (hamartoma)

This rare parathyroid lesion may cause confusion for the pathologist because the lesion shows a normal ratio of fat to parenchymal cells. Hence it is critical to know the size of the lesion. The tumors are often several grams in size, and one can discern the amount of parenchymal cell mass by calculating the percentage parenchyma versus total gland weight. When this is done, the parenchyma in such lesions is equal to that of a usual parathyroid adenoma.[28-30]

Cystic adenoma

Cystic change in a parathyroid adenoma is relatively common, but these are only microcysts. Gross cystic change is unusual but can occur in large (over 1 g) lesions that may be a hyperfunctional. The cysts contain parathyroid hormone.[31-34]

Double adenomas

The existence of this lesion was debated in the literature for years. With the advent of the routine use of intraoperative intact PTH (iPTH) measurement, it is clear that some patients have asymmetric multigland disease which presents as double adenomas as the cause of their PHPT. The estimated incidence of this presentation is 2%–7%. The most common combination of tumors involves the two upper glands. One of the lesions is usually smaller than the other,[35-37] and this may cause a false-positive result of the ioPTH test after excision limited to the larger adenoma.

Atypical parathyroid tumor

The definition of this lesion continues to be in flux. It is said to have some of the features of parathyroid carcinoma, but not all and thus is insufficient to render a malignant diagnosis. Most of these lesions are large, may show capsular invasion or invasion into surrounding fat, or show some mitotic activity. However, they do not demonstrate vascular invasion, necrosis, or invasion of neighboring organs. After excision, most atypical adenomas behave in a benign fashion, although a few have recurred in the neck.[38,39]

Hyperplasia

MGD is not rare; it is found in approximately 15% of patients with PHPT. Some patients will have four enlarged glands at initial presentation (synchronous), but some may have metachronous hyperplasia, and the true diagnosis of MGD is made late in the course of the disease following multiple operations. Hereditary variants of PHPT and lithium-induced PHPT show this type of pathology.[40-42]

Carcinoma

Parathyroid carcinoma is an extremely rare malignancy accounting for less than 1% of PHPT. The tumors at surgery are large and infiltrative; invasion of surrounding organs may be noted. Histologically, the tumors show bland and uniform cytology, but some are pleomorphic. Mitotic activity, necrosis, and invasive growth, including vascular invasion, are often seen. Parathyroid tissue that has metastasized is by definition malignant. Common sites, such as lung, bone, or liver, are seen in about 30%–50% of cases, but many affected patients die of the metabolic consequences of hypercalcemia. PHPT-jaw tumor syndrome shows parathyroid

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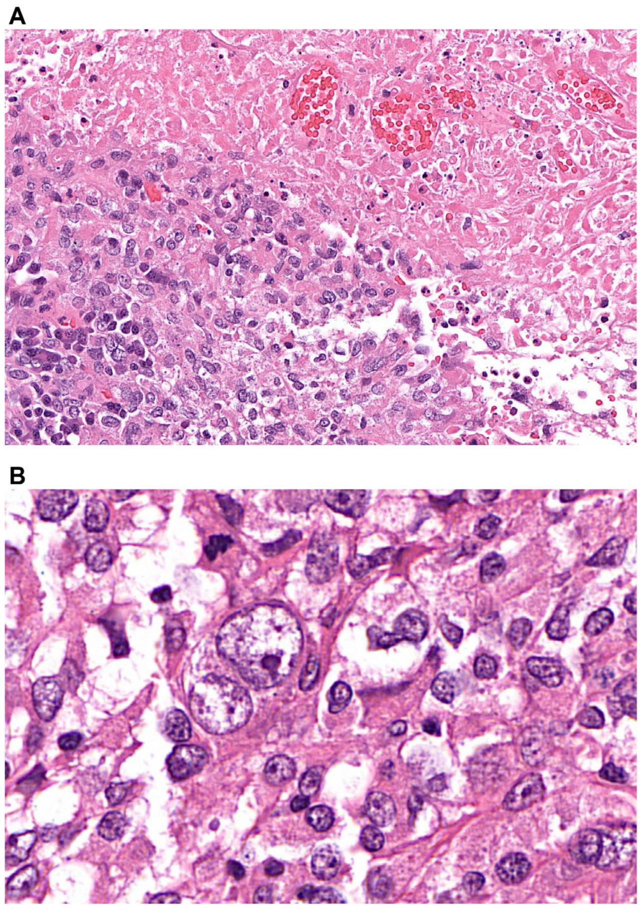

Fig. 2. (*A*) Nuclear pleomorphism, vascular invasion and invasion of adventitia of esophagus. (*B*) Parathyroid carcinoma with necrosis amid cellular parathyroid tissue.

carcinoma in 15% of affected patients, with tumors showing a thick capsule, sheet-like growth, eosinophilic cytoplasm, and perinuclear clearing. Rarely can parathyroid carcinomas be non-functional and present as a large mass in the neck. These tend to show oncocytic cytology and are aggressive lesions clinically (Fig. 2).[43-48]

Sequeleae of Biopsy and Surgery

Fine needle aspiration biopsy of a parathyroid gland is rarely, if ever, indicated owing to the risk of local implantation and seeding of parathyroid cells. The diagnosis of PHPT is a biochemical one, and tissue is not needed. Parathyroid carcinoma should not be biopsied if that diagnosis is suspected preoperatively. In rare cases of recurrent disease, fine needle aspiration for needle washout for PTH or cytology may be warranted to confirm parathyroid tissue location (ie, undescended).

Infarction

The apparent cure of PHPT following fine needle biopsy of a parathyroid gland is due to infarction of the adenoma. Usually a normal rim of viable parathyroid will persist, but the majority of the lesion will show infarction in the center.[49]

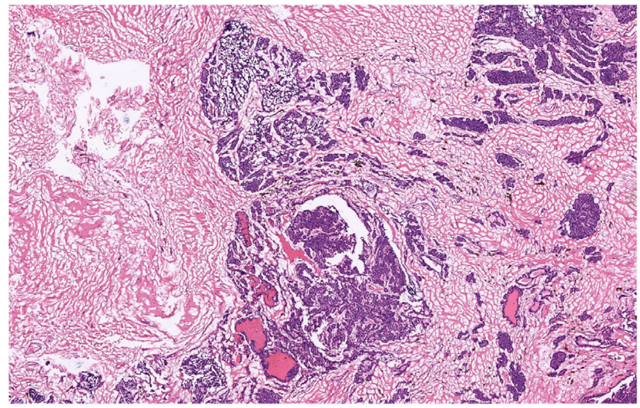

Fig. 3. Parathyromatosis. Note multiple small cellular fragments of parathyroid tissue in fibrous tissue. This tissue was located at lower pole of thyroid gland.

Parathyromatosis

Often a sequella of surgery for secondary hyperparathyroidism (due to renal disease), parathyromatosis can occur in the setting of PHPT as local recurrence due to capsular rupture of a benign lesion. The tissue “spills” into the surgical field and “takes”; subsequent growth of tiny foci of abnormal parathyroid that continue to hyperfunction causes persistent or, more often, recurrent hyperparathyroidism. It is difficult to cure because of the myriad and often microscopic nature of this proliferation (Fig. 3).[50]

Intraoperative Assessment during Parathyroid Surgery

Although some utilize the results of ioPTH assay to guide the extent of surgical resection,[51] others rely on intraoperative frozen section analysis.[52] It is often impossible to use a frozen section to diagnose whether a gland is an adenoma or hyperplastic. What can be expected is the identification of (i) the tissue as parathyroid, (ii) whether the parathyroid tissue appears normal or abnormal,[53,54] and (iii) whether the tissue is hypercellular. Incorrect identification is rare but can occur if the tissue is crushed and difficult to interpret and usually is definitively noted as either lymph node or thyroid.[55-57]

On occasion a parathyroid will have a rim of residual parathyroid tissue that abuts the totally or markedly cellular portion of the gland. This finding can allow the pathologist to favor the lesion as an adenoma (Fig. 4).

Parathyroid localization procedures to plan first-time surgery for sporadic primary PHPT

Should localization be performed? By whom? And when in the workup of PHPT?

Guidelines,[11,58,59] reviews,[7,60-62] and meta-analyses[63,64] agree that localization procedures are helpful and should be performed when considering surgical intervention for PHPT. They should not be performed to establish a diagnosis, but only to guide the surgical approach.[58] The majority of patients with

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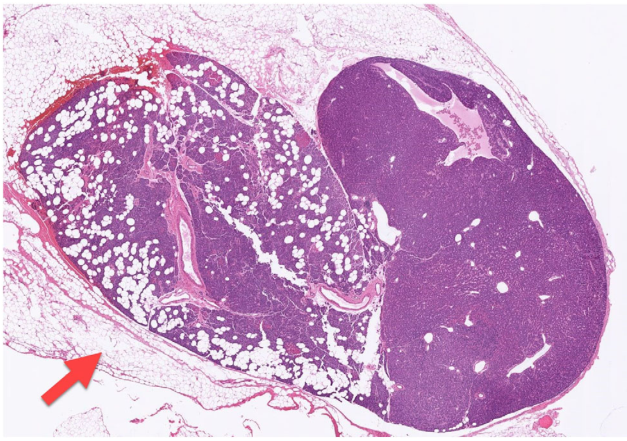

Fig. 4. Parathyroid adenoma, chief cell type. Note normal rim of parathyroid cellularity on left noted with red arrow.

PHPT have a single adenoma.[58] Removal of the diseased gland results in long-term definitive cure.[65] Imaging provides a roadmap to help minimize the dissection necessary to remove it, thereby shortening operating time, possibly also length of stay, and lowering the risk of complications,[66,67] resulting in reduced costs.[68] Patients with MGD-PHPT, such as MEN1, or receiving lithium are less likely to benefit from localization procedures.

What localization procedure(s) should be performed?

Currently, there is no universally accepted algorithm for localization procedures. Direct comparison of localization procedures is challenging due to significant heterogeneity in imaging protocols (ie, sestamibi with planar versus single-photon emission computed tomography [SPECT]), local radiologist expertise, and accuracy endpoints (ie, lateralization versus quadrant localization). Most experienced academic centers use ultrasonography or scintigraphy,[64] and concordant localization is associated with a very high (>97%) positive predictive value.[69,70] It is important to note that all localization procedures are less sensitive in detecting smaller, posteriorly located, or multiple adenomas compared to larger solitary adenomas.[71]

Ultrasonography of the neck is inexpensive, accessible, and radiation-free. Pooled studies have shown a high positive predictive value of 76%. Positive ultrasonographic findings are associated with a high chance of cure.[63] However, the diagnostic accuracy of ultrasound is dependent on the experience of the operator[63] and is limited for detecting smaller, deeper, and ectopic glands. Some have advocated that ultrasound should be performed by a surgeon,[72] but in centers where there are dedicated radiology teams, specialization is exceedingly efficient. In addition, ultrasonography has the advantage of identifying concomitant thyroid pathology that may need to be addressed during the same operation.

The advantages of scintigraphy include localization of ectopic glands, lower exposure to ionizing radiation compared to 4DCT, and common availability. The sensitivity and specificity of sestamibi imaging varies widely in the literature because many different sestamibi protocols are employed.[73] The predictive value for sestamibi-SPECT in pooled studies is 80%.[63,74] 4DCT has a higher sensitivity and specificity than ultrasound or scintigraphy,[75-79] with a predictive value >90%, but it has the disadvantage of having a higher radiation dose[80] and administration of CT intravenous contrast. Advantages include superior spatial resolution and improved anatomic delineation for surgical planning. Recent literature suggests that 4DCT is also superior to ultrasound and scintigraphy in more challenging clinical scenarios of MGD PHPT[81-83] and in reoperative parathyroid surgery.[76,84]

18-F fluorocholine positron emission tomography (PET) has emerged as a new tracer with possibly higher localization accuracy compared to other techniques compared to other mods.[85] A recent meta-analysis concluded that 18-fluorocholine PET was a promising new modality for PHPT and should be investigated further.[86] Currently, 18-fluorocholine is not approved in the USA.

MRI does not provide superior sensitivity and specificity than 4DCT and is not routinely used. Selective venous sampling, whereby the neck veins are sampled for measurement of PTH, is an invasive but accurate method.[87] Owing to its invasiveness, its role is predominantly limited to planning reoperative surgery when other imaging techniques are inconclusive.

In summary, all patients who are to have targeted PTX should have preoperative localization studies performed by dedicated radiologists. Whether more expensive tests will replace the widely implemented combination of ultrasound plus a sestamibi scanning, and whether they should be performed if this initial approach does not localize a parathyroid adenoma, rather than to proceed to a bilateral exploration, should be further investigated.

What should be done if localization procedures are negative, ie, *do not show any parathyroid lesions, or discordant*, ie, *if two or more localization procedures show different localizations of parathyroids?*

Every localization procedure has its strengths and limitations. All available imaging should be reviewed by the surgeon before proceeding to operation. Some scans interpreted as negative can be interpreted by an experienced surgeon as positive when reevaluated.[88] High-volume centers have better accuracy in imaging studies, and it seems reasonable to repeat negative imaging tests "in house" in patients referred from less experienced units.

There is consensus that the results of localization studies should not be used as an indication for surgical intervention but rather for deciding and planning a selective or a bilateral procedure. However, data indicate that the failure rate (ie, the rate of persistent hypercalcemia after surgery) is increased in patients with negative imaging. Data from a European database for endocrine surgery (Eurocrine®) of 5186 patients operated on for PHPT showed that the odds of persistent disease were increased by 2.5-fold in patients with negative ultrasound and 1.6-fold in patients with negative scintigraphy.[70] The risk of persistent disease is further increased if an operation is performed without access to ioPTH.

Is ioPTH monitoring useful for ascertaining cures in patients with a single parathyroid adenoma localized with two positive imaging techniques?

ioPTH determination was proposed to detect a drop of iPTH levels during selective PTX that guarantees a long-term cure. The magnitude of this decrease and the timing of blood sampling before and after single adenoma resection vary according to the various published criteria. As an example, the Miami

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criterion, which requires a ≥ 50% drop from the highest preexcision or preincision PTH value at 10 minutes post gland excision),[89] is used as an indicator that all hyperfunctioning parathyroid tissue has been adequately excised. A protocol requiring the normalization of PTH levels has marginally better results in terms of cure but longer waiting time and more unnecessary contralateral explorations.[90]

Whichever test is used, a significant drop of iPTH obviates the need to explore the contralateral side to seek other hyperfunctional tissue. ioPTH has been enthusiastically embraced by many centers owing to the purported advantage of improved cure rates.[8,91-93] However, although the high accuracy (>95%) of ioPTH for correctly predicting the outcome, namely, a single parathyroid adenoma, is well accepted, its routine use as an adjunct during selective PTX for PHPT remains a topic of debate.[94] Proponents cite the advantage of receiving immediate confirmation of adequate resection of all hyperfunctioning tissue at the time of operation and argue that the omission of ioPTH risks missing MGD and decreases the likelihood of achieving biochemical cure.[95,96] However, the accuracy of ioPTH may be reduced in the setting of MGD and, because most PHPT is caused by single-gland disease, some have questioned the utility of this modality in cases where a pathological gland has been localized by two concordant imaging techniques.[94,97-99] Thus, a central argument against the routine use of ioPTH in patients with concordant preoperative imaging is that it provides limited added value in this setting and that a marginal improvement in cure rates is not justified by the increased operating room time and financial cost.[100] Other drawbacks of ioPTH include the risk of a false-negative result (when iPTH levels do not fall despite the removal of the only pathological gland), which may lead to unnecessary bilateral neck exploration. A false-positive result (when iPTH levels fall to a level indicating cure but the patient remains hypercalcemic postoperatively) may be especially problematic in the presence of double parathyroid adenomas. Up to two-thirds of these patients can have an apparent "curative" decline in iPTH levels after resection of the first tumor.[37,101-103] This is thought to occur when the larger dominant adenoma is resected first, leaving behind a temporarily suppressed second adenoma that is not active and, thus, not appreciated by ioPTH at the time of surgery.[37,103]

Studies describing patients who underwent selective PTX using or not using ioPTH were revealed by a search to be eligible for review (Fig. 5). Of the 27 included studies, 12 comprised only patients with two concordant preoperative localization techniques.[96,97,104-113] The remaining 15 studies included patients with one positive imaging study or discordant localization, but results for the imaging concordant subgroup were reported separately, and these were included.[95,98,114-126] Twenty-three of the 27 studies were retrospective cohort studies,[96-98,104-108,110-113,116-126] whereas 4 out of 27 were prospective observational studies (Table 1).[95,109,114,115] There were no randomized controlled trials comparing ioPTH with no IoPTH in patients with concordant preoperative imaging.

A total of 5297 patients with PHPT and two concordant preoperative imaging techniques were included in these 27 studies: 3307 with ioPTH and 1990 without ioPTH. In all these studies, concordant imaging was defined as a single adenoma localized by both functional (usually Sestamibi) and anatomical (usually ultrasound) imaging techniques. Twenty-one studies defined concordance based on dual preoperative imaging with ultrasound and MIBI scintigraphy,[97,98,104,105,109-126] Four studies defined concordance based on ultrasound and MIBI-SPECT,[95,96,107,108] one study used ultrasound with 4DCT,[106] and one study used 18F-fluorocholine PET/CT.[117]

All 27 studies reported postoperative cure rates ranging from 90.3% to 100% with ioPTH and 91.9% to 97.8% without ioPTH. The postoperative cure rate ranged from 96.7% to 99.6% with ioPTH and 91.9% to 97.8% without ioPTH. In 18 studies in which ioPTH was used, its value-added accuracy (ie, the percentage of cases in which a <50% decline in PTH appropriately resulted in conversion to a bilateral neck exploration) ranged from 0% to 6.1%. False-positive and false-negative rates ranged from 0% to 3.3% and 0% to 16.7%, respectively.[96,97,104-108,114,116,119-121,123-125] In addition, ioPTH adds an average of 30.9 minutes per case[126] and incurs an additional cost of around USD 520 per patient.[124]

In summary, ioPTH is likely associated with a marginal increase in cure rate for patients with sporadic PHPT who have a strong suggestion of single-gland disease localized on two concordant imaging studies. In this setting, ioPTH adds value to surgical decision-making during selective PTX in only a small proportion of cases (≤6%), at the expense of additional cost, longer operative time, and unnecessary contralateral explorations. The role of good surgical judgment cannot be understated, and, although ioPTH can be a valuable adjunct in patients with nonconcordant preoperative localization and in select reoperative cases,[114] its routine use in patients with two high-quality concordant imaging studies is not essential.

Pre- and postoperative care

Hungry bone prevention and management

Hungry bone syndrome is characterized by severe and prolonged hypocalcemia, hypophosphatemia, and hypomagnesemia, following PTX for very advanced PHPT. The underlying mechanism is the rapid net influx of calcium into bone after elimination of PTH-stimulated osteoclastic resorption.[127] Untreated, hungry bone syndrome leads to paresthesias, neuromuscular irritability, tetany, and, rarely, congestive heart failure. It is generally observed in patients with elevated markers of bone turnover and overt skeletal manifestations of PHPT that are visible on plain radiography.[128] The prevalence of hungry bone syndrome was reported at 13% in 1988, though the rate is likely much lower today given the progressive shift toward the discovery of clinically and biochemically milder PHPT over time. The post-PTX hungry bone prevalence is higher in patients with radiological bone disease, for both PHPT and severe secondary hyperparathyroidism (eg, the hyperparathyroidism of renal failure).[129] In patients with high BALP concentrations (indicative of high bone turnover) and overt bone disease, starting treatment with calcitriol the day before surgery may be useful to prevent clinical hypocalcemia. Management of hungry bone syndrome consists of aggressive (often intravenous) supplementation of calcium, calcitriol, and magnesium.[127,130]

Parathyroid crisis (acute PHPT)

Parathyroid crisis should always be considered in the differential diagnosis of acute hypercalcemia. It is a rare, life-threatening complication of PHPT characterized by s-Ca >14 mg/dL (often also characterized by a rapid increase in the serum calcium concentration over a short period of time), altered mental status, severe dehydration, and decreased renal function.[131] Left untreated, the condition can lead to death from cardiac arrest, renal failure, pancreatitis,[132] or complications of coma. Treatment consists of intravenous

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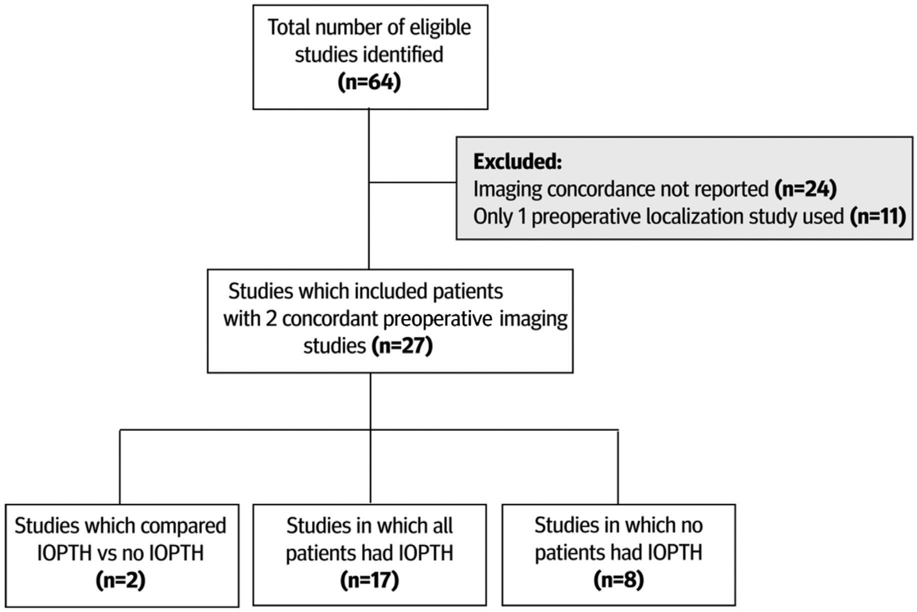

Fig. 5. Flow diagram showing selection of articles for review.

hydration, loop diuretics (only after hydration has been achieved), and urgent PTX. Medical management with bisphosphonates (most often intravenous pamidronate or zoledronic acid) and sometimes dialysis may temporize parathyroid crisis and serve as a bridge to definitive surgical management.[133,134] When parathyroid crisis occurs, it is often against a backdrop of the common, milder form of the disease. Surgery is always indicated in these patients, either at the time of the crisis, if standard nonsurgical measures are not successful, or soon thereafter when the patient is more stable.

Outpatient surgery

As transient mild hypocalcemia can usually be managed on an outpatient basis using oral medications, same-day discharge after selective PTX has gained popularity. The length of stay following PTX is principally driven by the remote risk of postoperative neck hematoma (<1% of patients), and usually manifests within 6 hours. Same-day discharge is safe in appropriately selected patients,[58] especially those who have had straightforward selective PTX. In patients with concurrent medical issues, it is sometimes prudent to arrange for an overnight stay after the surgery.

Indications for calcium and vitamin D supplementation at discharge

Patients at risk of postoperative hypocalcemia are those presenting with severe hypercalcemia, elevated BALP or C-telepeptide of type 1 collagen (CTX) if available, subtotal PTX, and reoperative cases in whom previous normal glands may have been excised or injured.[135] In these circumstances, scheduled prophylactic postoperative calcium regimens (1–3 g) with or without vitamin D metabolites (calcitriol at 0.5–1 mcg/24 hours or comparable doses of 1-alfa calcidiol) should be administered. Normalization of vitamin D levels may improve BMD in patients with concomitant PHPT and vitamin D deficiency.[136]

Reoperative surgery

Persistent disease usually represents missed pathology, and recurrence denotes newly developed pathology. Persistent PHPT is defined as failure to achieve a durable eucalcemic state for 6 months after PTX. The most common causes of this are a missed adenoma, a second adenoma after selective PTX, or incomplete surgery in MGD. If at 6 months the patient is eucalcemic and then later becomes hypercalcemic again, then this is defined as recurrent disease.[137] This may be due to additional (fifth or more) enlarged glands in hereditary PHPT, parathyroid cancer, or local recurrence of a partially resected adenoma. Accordingly, the first "localization" procedure before redo surgery is to review the previous imaging, surgical notes, and pathology because they often give a clue as to how to proceed with the next operation. Preoperative imaging is essential before reoperation for persistent or recurrent PHPT with a combination of imaging modalities and concordance of at least two tests.

Imaging modalities

Ultrasound can miss glands deep in the mediastinum, tracheoesophageal groove, para- and retroesophageal regions, and in obese patients. Interpretation is key because in fact a negative study can be quite informative if, for instance, persistent disease exists in an obese patient with poor hyperextension. Ultrasound-guided fine needle aspiration with PTH assay of equivocal central and lateral neck lesions is effective for the localization of parathyroid lesion in reoperative surgery.[138]

Sestamibi scintigraphy as a single modality has relatively poor performance, with accurate localization in only 19%–33% of patients,[139,140] even with the addition of SPECT/CT. The addition of ^{123}I to sestamibi for dual-isotope subtraction scintigraphy

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Table 1. Overview of Studies of Selective PTX with or without IOPTH in PHPT Patients with Two Concordant Preoperative Localization Techniques

Study/year	Study design	Total *N* of patients	*N* with 2 concordant preoperative studies	*N* with concordant imaging who underwent ioPTH	*N* with concordant imaging who did not have ioPTH	Cure rate in ioPTH group (%)	Cure rate in non-ioPTH group (%)	Percentage value-added accuracy of ioPTH	FP rate of ioPTH (%)	FN rate of ioPTH (%)	ioPTH criteria used	F/U, months, mean (range)
Studies which directly compared IOPTH versus no ioPTH												
Barczynski (2007)[114]	P	177	119	78	41	99.1	91.9	3.8	0	0	M	27.8 (6–42)
Sartori (2019)[97]	R	426	426	212	214	97.6	96.3	2.4	2.4	2.4	V	6[a]
Studies in which all patients underwent ioPTH												
Barczysnki (2009)[104]	R	260	260	260	0	99.6	N/A	3.1	0.4	2.3	MM	26 (6–66)
Bobanga (2017)[96]	R	127	127	127	0	100	N/A	6	0	0	MM	4 (0.2–122)
Garbutt (2016)[115]	P	341	194	194	0	97.9	N/A	N.R.	N.R.	N.R.	M	6[a]
Gawande (2006)[105]	R	322	322	322	0	99	N/A	1	1	0	M	1[a]
Heineman (2015)[106]	R	169	169	169	0	98	N/A	4.1	1.8	8.3	MM	N.R.
Helbrow (2016)[116]	R	78	51	51	0	94.6	N/A	3.8	0	7.5	M	1[a]
Lombardi (2008)[107]	R	207	207	207	0	90.3	N/A	2.4	2.4	4.8	M	14.1(1–29)
Miura (2002)[119]	R	115	39	39	0	97.4	N/A	3	2.6	7.7	M	11 (2–28)
Nair (2016)[120]	R	143	121	121	0	96.7	N/A	1.7	0.8	2.5	M	6[a]
Najafian (2017)[121]	R	342	83	83	0	98	N/A	2	1.2	1.2	M	N.R.
Pradhan (2019)[122]	R	83	57	57	0	98.2	N/A	1.8	0	0	M	6[a]
Riss (2009)[108]	R	338	338	338	0	97.9	N/A	4.4	2.1	0	V	45.5 (24–108)
Sakimura (2013)[123]	R	60	56	56	0	100	N/A	0	0	16.7	M	N.R.
Shawky (2018)[124]	R	617	393	393	0	98	N/A	6.1	1.9	0.3	M	6[a]
Siperstein (2004)[95]	P	350	205	205	0	91	N/A	3	N.R.	N.R.	M	10 (0.3–47)
Smith (2009)[125]	R	428	209	209	0	97	N/A	3	3.3	1.4	M	N.R.
Zawawi (2013)[126]	R	211	186	186	0	94.6	N/A	1.1	N.R.	N.R.	M	N.R.
Studies in which no patients underwent ioPTH												
Arici (2001)[98]	R	338	105	0	105	N/A	96.2	N/A	N/A	N/A	N/A	N.R.
Cho (2011)[109]	P	119	119	0	119	N/A	97	N/A	N/A	N/A	N/A	1[a]
Haciyanli (2009)[110]	R	30	30	0	30	N/A	96.7	N/A	N/A	N/A	N/A	16 (3–55)
Hocevar (2016)[117]	R	151	126	0	126	N/A	96.8	N/A	N/A	N/A	N/A	N.R.
Kim (2015)[118]	R	53	39	0	39	N/A	94.9	N/A	N/A	N/A	N/A	6[a]
Mihai (2006)[111]	R	150	150	0	150	N/A	97.3	N/A	N/A	N/A	N/A	16 (3–48)
Mownah (2015)[112]	R	146	146	0	146	N/A	97.3	N/A	N/A	N/A	N/A	6[a]
Suliburk (2010)[113]	R	1020	1020	0	1020	N/A	97.8	N/A	N/A	N/A	N/A	6[a]

Abbreviations: FP, false positive; FN, false negative; F/U, follow-up; ioPTH, intraoperative parathyroid hormone monitoring; M, Miami criteria; MM, modified Miami criteria; *N*, number; N/A, not applicable; N.R., not reported; P, prospective; R, retrospective; V, Vienna criteria.

[a]Time point at routine post-operative calcium check stated, but mean follow-up duration not specified.

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improves accuracy to 59%.[139] A combined ultrasound and sestamibi strategy[141,142] accurately localized the culprit adenoma in 94% of patients with persistent disease.[141]

In the reoperative setting, 4DCT has a 77%–95% higher sensitivity for the localization of parathyroid adenoma alone[76,84] and compared with traditional imaging modalities.[143,144] ^{18}F-fluorocholine PET/CT had a higher sensitivity compared to 4DCT (85% versus 63%, respectively) in one series[145] and localized adenomas in 58% of patients with negative localization.[146] ^{18}F-fluorocholine PET/MRI also has high sensitivity when other imaging studies are inconclusive. However, the disadvantages of fluorocholine PET imaging include higher costs and limited availability compared to other imaging tests.[147]

Previously, selective venous sampling was deemed a valuable localization when initial imaging localization studies are equivocal or nonlocalizing.[148,149] It is now rarely performed because it is invasive and requires a skilled interventional radiologist and so is usually reserved for challenging reoperative surgery.

Surgical expertise

Surgery performed at high-volume centers correlates with a reduced need for reoperation.[150,151] In a recent French multicenter study, low-volume parathyroid surgery was included among the factors predicting the need for reoperation: with an average annual caseload of 31 PTXs, the rate of redo surgery was 3.2% for low-volume centers, but the rate dropped to 2.0% for high-volume centers.[152] Lower rates of avoidable reoperations for persistent/recurrent PHPT have been observed in the hands of high-volume surgeons (13%–22% versus 78%–89%).[153] Similarly, low-volume surgeons were significantly more likely to miss a parathyroid adenoma in a normal anatomic location.[154] Most studies show that PTX performed in a high-volume setting achieves cure rates of >95%.[155]

Intraoperative adjuncts

Some intraoperative adjuncts have been proposed to ensure the success of PTX. This section reviews the role of gamma camera, gland aspiration, and ultrasonography (USG). The role of ioPTH measurements has already been described.

Intraoperative gamma probe

The use of a gamma probe for selective PTX was proposed to detect Tc99m-sestamibi being retained in hyperfunctioning parathyroid glands during surgical procedures.[156] Protocols include the injection of 10–25 mCi (740–925 MBq) Tc99m-sestamibi within 1–3 hours of the operation. The activity is based on obtaining background counts and then achieving higher counts over the suspected gland. Gamma probes translate focus intensity into count rate and audio signaling but do not guarantee a more precise localization than conventional imaging. The added hassles of timing, injection, and equipment have not added to the success of gland localization.

Gland aspiration

This adjunct is often considered as a kind of "biochemical frozen examination" of a presumed, excised adenoma[157] and is an efficient way of differentiating parathyroid from nonparathyroid tissue upon excision. It is carried out by aspirating the excised tissue with a fine needle; the aspirated material is then washed with 1 mL of saline, and its content is measured for iPTH. Typically, the PTH aspirated from a parathyroid adenoma yields a concentration >1500 pg/mL. This method was shown to be efficient and cost-effective, with both sensitivity and specificity close to 100%.[157-159]

Ultrasound

Intraoperative ultrasound has the distinct advantage of being able to be used preoperatively and then again during the course of the surgery to locate the previously identified parathyroid gland. On the operating table with the patient positioned, ultrasound allows the surgeon to place the most suitable small incision for that specifically localized adenoma (Fig. 6). This can be particularly advantageous when resecting undescended glands high in the neck near the jaw.[160]

PTX for conditions and situations where MGD is anticipated

The majority of patients with MGD suffer from hereditary syndromes. The goal of treatment of patients with MGD-PHPT is to durably restore s-Ca and PTH to normal while preventing hypoparathyroidism and reoperations.[161] Traditionally, a reoperation in this setting was considered a failure. With the shift of goals and expectations and the available imaging studies, an initial, less aggressive resection was considered in a select subgroup of patients with MGD. The surgery should balance potential risks and the avoidance of permanent hypoparathyroidism.[5]

Lithium-Induced Multigland Hyperparathyroidism

Pertinent clinical history includes inquiring about a history of prolonged lithium use, a drug commonly used to treat bipolar disease. The full-blown clinical picture often includes, in addition, nodular thyroid disease and renal insufficiency. Lithium-associated PHPT has been reported to have a higher (60%) chance of having MGD.[162] Because of this, the approach has been controversial. However, if preoperative imaging localizes to a single adenoma and ioPTH monitoring is available, a focused approach may still be pursued.[13,163] In a study of 1207 patients, the incidence of lithium-associated hyperparathyroidism was 1.3%. Of those, 12 out of 16 (75%) had a single adenoma removed and had a durable cure. Based on this, the recommendation is that a directed approach is possible if the decision of when to stop the operation is based on ioPTH monitoring.[163]

Multiple Endocrine Neoplasia Type 1

MEN1-PHPT is characterized by an early onset, even during adolescence. The lifetime penetrance is 100%. These patients are regularly screened, and the indication for PTX is either symptoms or elevated s-Ca. Preoperative imaging studies rarely contribute to initial surgical planning but may, on rare occasion, detect ectopic glands. A classic bilateral neck exploration with the identification of all four parathyroid glands has been the preferred procedure for the last three decades,[164] aiming at resection of 3.5 glands, leaving a well-vascularaized remnant of about 50 mg or, if present, a normal gland marked with an irreabsorbable suture. A bilateral cervical thymectomy is also recommended because of the 15% chance of having a parathyroid tissue within the thymus and the chance of having a thymic

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Fig. 6. The anterior border of the sternocleidomastoid muscle (SCM) is noted by the discontinuous line and the angle of the mandible as the main anatomical landmarks to access a previously imaged left undescended parathyroid adenoma (courtesy of AS-S).

carcinoid tumor (very rare and with male predominance).[5] A 13% recurrence rate at 7 years has been reported after properly performed subtotal PTX, with half of these occurring on the remnant and half on a supernumerary gland.[23] The so-called unilateral neck clearance strategy is aided by imaging studies and is currently under investigation. The rationale for this approach is that MEN1-PHPT may occur in different patterns because of the fact that different germline mutations result in different numbers and sizes of parathyroid glands involved. In addition, it eliminates the risk of hypoparathyroidism after first-time surgery.[165] If this approach is chosen, two concordant imaging studies identifying an affected gland, the ipsilateral gland and the thymus can be removed, leaving an untouched contralateral side. An ioPTH assay is recommended with this strategy.[5] Conservative approaches to MEN1-PHPT should be closely monitored since performing less than subtotal PTX is associated with high relapse rates.[6,14] A third, radical, approach, consisting of total PTX with autotransplantation, has been occasionally implemented in some units but it carries a high rate (30%–50%) of protracted and permanent hypoparathyroidism.[166,167]

Several suggestions have been made for further exploration genotype–phenotype relation to select patients for a less than subtotal PTX since genetic heterogeneity will eventually help to predict the aggressiveness of parathyroid disease.[5] Examples are nonsense or frameshift mutations in exons 2, 9, and 10.[14] Recently it was shown that menin, the product encoded by the *MEN1* gene, also regulates the expression of micro RNAs, such as let-7a, mir-155, mir-4258, mir-664, and mir-1301, with a possible role either in tumorigenesis or in the clinical behavior of the parathyroid tumors.[168]

Multiple Endocrine Neoplasia Type 2

MEN2-PHPT is considered to be an infrequent syndromic variant only occurring in MEN2A. When enlarged parathyroid glands are encountered during surgery for medullary thyroid cancer, they should be removed. Otherwise, surgical intervention is recommended only when patients are symptomatic or have elevated serumCa. Recently a tailored PTX was suggested based on concordant preoperative imaging studies.[169] Recurrence is less common compared to MEN1-PHPT.

Hyperparathyroidism-Jaw Tumor (PHPT-JT)

PHPT-jaw tumor (JT) is a rare autosomal dominant syndrome, more recently described as CDC-73. It has incomplete penetrance and variable expression. It is characterized by different and often metachronous parathyroid gland involvement and occurs at an early age. PHPT-JT has a relatively high prevalence of carcinomas, atypical adenomas, and ossifying fibromas of the mandible or maxilla.[170] The optimal surgical strategy for PHPT-JT is still under debate, however, and a tailored strategy, as in sporadic PHPT, seems to be justified. If imaging studies are negative, however, bilateral neck exploration is recommended.

Familial Isolated Hyperparathyroidism

Familial isolated hyperparathyroidism is a rare, nonsyndromic form of hereditary PHPT known for its early onset of disease. It is caused by an atypical germline inactivation, isolated to the intracytoplasmic tail domain of the *CASR* gene. Due to its rarity, there is a lack of evidence-based surgical strategy. An empirical approach, based on concordant preoperative imaging studies, is recommended.[170]

Neonatal Severe Hyperparathyroidism (Nshpt)

Neonatal hyperparathyroidism is a very rare, extreme form of familial hypocalciuric hypercalcemia (FHH) caused by homozygotic mutations of the FHH gene. Clinical presentation occurs shortly after birth with life-threatening hypercalcemia and hypocalciuria. The affected parathyroid glands are hyperplastic and hypercellular at pathological evaluation.[168] After urgent treatment with intravenous saline and biphosphonates, a total PTX should be performed to prevent a fatal outcome in these patients. More recent case reports have also suggested a role in select patients for cinacalcet treatment to delay or potentially avoid PTX.[171]

Autosomal Dominant Mild Hyperparathyroidism

This nonsyndromic form of hereditary PHPT is also very rare and resembles Familial Isolated Hyperparathyroidism. It is caused by an atypical germline inactivation, isolated to the intracytoplasmic tail domain of the *CASR* gene. Treatment is tailored, based on concordant preoperative imaging studies.[168]

Should osteoporosis be treated with antiresorptive drugs after PTX for PHPT?

It is estimated that 34% to 48% of patients with PHPT have osteoporosis in regions where the mild form of the disease predominates.[172,173] Excess parathyroid hormone increases bone resorption, with a consequent reduction in BMD and strength and an increased risk of fractures. Khosla et al.[174–178] reported that patients with a mild form of PHPT have a higher risk for pelvic, Colles, rib, and vertebral fractures compared to the general population. It should also be considered that PHPT predominates

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in postmenopausal women and that it is not possible to segregate the impact on BMD of the disease itself from that due to aging and gender. These last variables were independent predictors of fracture risk in the Khosla cohort.[177]

The only curative treatment of PHPT is PTX.[179] Many patients who undergo surgical intervention show gains in BMD.[180,181] Successful PTX also leads to an increase in BMD in younger patients with more severe disease reducing the risk of fractures.[182-185] Early surgery after the diagnosis of PHPT is made is desirable since prolonged observation leads to further BMD loss, even in mild cases.[186,187] In a study[188] involving 145 patients with mild disease, a decrease in bone turnover markers and an increase in BMD at spine and hip were observed 5 years after surgery compared to an observation group. A controlled trial performed in a Japanese population[189] showed a sustained increase in trabecular and cortical BMD 6 years after PTX. VanderWalde et al.[190] compared the fracture risk in 533 patients with PHPT undergoing either surgery or observation over 10 years. PTX decreased the risk of fractures in osteoporotic, osteopenic, and normal BMD patients, with the largest impact on the former group. PTX was associated with fracture risk reduction,[191] even in patients without criteria for surgery according to current guidelines.

An improvement in BMD is expected to occur after successful PTX, particularly in patients with osteoporosis, good renal function, and high adenoma weight.[192] BMD will remain stable or sustain minimal losses in half of the postmenopausal women with better baseline BMD, this being independent of the ALP and vitamin D status (calcifediol and calcitriol).[192] The reduction in fracture risk appears to be particularly significant the first year after PTX.[175] In patients with prior fractures, the risk appears to remain considerably high even after PTX.[184] As previously mentioned, postmenopausal women are the most affected population by both PHPT and "idiopathic" osteoporosis,[193-195] and they naturally experience increased risk of fractures.[196,197] Moreover, PHPT patients suffer vertebral fractures with a higher spine BMD than osteoporotic patients without PHPT,[198] probably because of worse bone quality.[199,200] Therefore, in individuals with advanced osteoporosis, it would be reasonable to start an antiosteoporotic medication to accelerate and optimize BMD gains after successful PTX in selected osteoporotic and aged patients. This option, however, is tempered by the expected gain in BMD that occurs regularly after PTX, without any pharmacological intervention. Moreover, the use of antiresorptive medications will reduce not only bone resorption but also bone formation,[201] thereby potentially impairing the robust bone formation that occurs after PTX. It is, thus, attractive to postpone the decision to intervene with medications until the 1- or 2-year postoperative BMD is obtained.

Data regarding the use of antiosteoporotic drugs after PTX are very sparse. Orr et al.[202] compared the risk of fractures and BMD changes in 1737 PHPT patients with treatment-naive osteoporosis divided into five treatment groups: observation, bisphosphonate alone (BPP), PTX (PTX), BPP then PTX (BPP-PTX), and PTX followed by BPP 2 years after surgery (PTX-BPP). Both BPP-PTX and PTX groups had a decrease in fracture incidence (45% and 54% reduction, respectively) compared to the observation group, whereas there was no significant fracture risk difference among BPP, PTX-BPP, and observation groups.

In summary, the limited data available do not support starting or continuing antiresorptive medication at least within the first 2 years following successful PTX in PHPT patients with osteoporosis. Further research is needed to elucidate how long after curative PTX the initiation of a medication would be additionally beneficial and which parameters would be useful to help in this decision.

Surgical expertise and postoperative complications

Volume/outcome results

A clear relationship between higher case loads and better outcomes in parathyroid surgery[203-205] has been consistently reported. Outcomes and definitions of surgical volume, however, are heterogeneous. Although some authors assess surgeons' volume, others assess hospital volume. The threshold used to define case loads varies from 10 to 100 annual cases for high-volume and 1 to 50 for low-volume centers. Arbitrary cut-off categorization has been used by almost all authors. Exceptionally, more accurate approaches, such as subdivision in quantiles[203] or mathematic formula correlating outcomes and volume,[150] were applied. A recent review suggests a threshold of 40 and <15 annual PTXs as cut-offs for the high-volume and low-volume parathyroid surgeons, respectively.[206] Hospital volume appears to be less important, and it is the workload, expertise, and experience of the individual surgeon that appears relevant.[204,207] Irrespective of this definition range, the majority of authors and international guidelines recommend concentrating parathyroid surgery in high-volume settings where surgeons have an appropriate case load and experience in the management of PHPT whenever feasible.[58,206]

Vocal cord palsy and hypoparathyroidism

Low-volume thyroid and parathyroid surgery carries a fourfold increase in overall morbidity.[203,205,208,209] The technical/surgical complication rate was significantly lower after PTXs performed by high-volume surgeons (1.91%–4.4% versus 1–3.5%).[150,204] This applies not only to first-time but also for redo surgery, with higher rates of complications in low-volume settings (3.8% versus 1.48%).[204] Vocal cord palsy (0.2% versus 1.6%)[153,209] and postoperative hypoparathyroidism (4% versus 14%) were less common in patients under the care of high-volume surgeons.[205,206,210] Regarding readmissions, some authors found no differences in 30-day readmissions between low- and high-volume centers (4% versus 4.2%),[209] whereas others reported that readmission was significantly higher for patients managed by low-volume surgeons (4.6% versus 1.5%).[208] In this last study patients operated for both thyroid and parathyroid cancer were included in the analysis.

Bleeding and infection

Among more general risks for parathyroid surgery are bleeding, infection, and deep venous thrombosis. Fortunately, the rates for each of these complications are exceptionally low.[211] Bleeding is a complication that occurs mostly in the form of postoperative hematoma and is reported in the literature to occur in 0%–1.6% of cases.[212] No perioperative risk factors have been identified to predict those patients who will develop neck hematomas.[213] A targeted or unilateral approach minimizes the risk of airway compromise because, hypothetically, one side of the airway would become congested. Caution is generally advised with patients who take anticoagulants or who have undergone more extensive dissection. With a significant hematoma, patients usually develop sudden neck swelling, pain or pressure, or dysphagia

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and may even have respiratory distress. Surgical reexploration to evacuate the source of hematoma is indicated for the management of a symptomatic hematoma. Various sources of bleeding exist from major vessels, reopening of cauterized veins, and oozing from surfaces touched during dissection, and all can be aggravated by hypertension, wretching, coughing, or vomiting during extubation or in the perioperative period. Management of postoperative neck hematomas includes close observation, early detection, airway management, and appropriate surgical intervention. Although bedside evacuation of a neck hematoma may be necessary for impending airway closure, this intervention may not be ideal for patients who are hemodynamically stable, able to talk, maintain oxygenation, and be safely transported to the operating room, where more resources for airway management are available. The majority of hematomas that require surgical evacuation occur by 4–8 hours after surgery and nearly all within the 24-hour postoperative timeframe, with few cases (10%) developing beyond 24 hours.[212]

Infection is rare (0%–0.11%), and prophylactic antibiotics are generally not indicated for initial parathyroid operation, although practice patterns vary widely in antibiotic administration.[214]

Recommendations and Future Directions

A multidisciplinary international task force has extensively reviewed the current surgical aspects of PHPT. This working group has had the opportunity to identify gaps in knowledge. These include addressing an update of definitions of recurrent and persistent disease. Previously, persistence was defined as missed disease with persistent or returning hypercalcemia within 6 months of surgery, and recurrence was defined as newly developed pathology with a normocalcemic period of at least 6 months. These time periods deserve to be reconsidered. In light of the better understanding of asymmetric hyperplasia and the information gained from more sensitive third- and fourth-generation PTH assays and ioPTH monitoring, a better understanding of dormant disease is needed. Conservative strategies for the treatment of MEN1-PHPT should be closely scrutinized over the long term. Acontemporary review of complications, including but not limited to recurrent laryngeal nerve injury in the era of magnified optics and increased electrothermy, should be analyzed. The observation of increased risks of complications in combined thyroid and parathyroid procedures should be reviewed and better described. Risk factors for parathyromatosis and local recurrence would be beneficial. The timing of initiating medical therapy for osteoporosis after successful PTX needs more elaborate study. In addition, identifying which patients may need antiosteoporosis therapy if trabecular bone loss occurs yet distal radius mass is maintained, before being cured surgically. Moreover, improved treatments for parathyroid carcinoma are warranted. The role of whole genome sequencing, personalized care, and immune therapy should be investigated.

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Author Contributions

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Ethical Statement

These papers are retrospective reviews and did not require ethics committee approval.

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Data Availability Statement

The data that support the findings in this study are openly available in PubMed, MEDLINE, EMBASE, and the Cochrane databases.

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