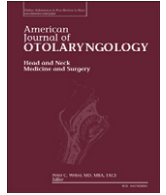




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Review Article

## Parathyroidectomy for tertiary hyperparathyroidism: A systematic review☆☆☆



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ABSTRACT

**Objective:** Analyze the efficacy and indications for parathyroidectomy as an intervention for tertiary hyperparathyroidism.  
**Data sources:** PubMed, MEDLINE, and Cochrane Library databases.  
**Review methods:** A systematic literature search was performed using the. Original research articles in English were retrieved using the search terms (“tertiary hyperparathyroidism” OR “3HPT”) AND “parathyroidectomy”. Articles were analyzed in regards to their surgical indications, operative endpoints, comparison between different surgical interventions, characterization of disease recurrence rates, and evaluation of alternative medical management.  
**Results:** Thirty studies met the criteria for inclusion. Among the studies that report indications for parathyroidectomy, persistent hypercalcemia as well as clinical manifestations of hypercalcemia despite medical therapy predicted which patients would eventually need surgical intervention. The majority of studies comparing the extent of parathyroidectomy recommended a more focused approach to parathyroidectomy when warranted. All studies found that parathyroidectomy was an effective treatment for 3HPT. Three studies discussed alternative conservative approaches.  
**Conclusion:** Interestingly, hyperparathyroidism alone is not an indication for surgery without other findings; rather, symptomatic hypercalcemia appears to be the main indication. Most studies recommend limited or subtotal parathyroidectomy for 3HPT. The operative endpoint of surgery is not necessarily a return of PTH to normal, but a >50% drop in PTH level even if PTH remains above normal. Additionally, “success” or “cure” is defined as normal calcium levels regardless of whether or not PTH is elevated. It appears the goal of surgery for 3HPT is not a normal PTH value, but a normal calcium level at least six months postoperatively.

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## 1. Introduction

Tertiary hyperparathyroidism (3HPT) represents a challenging case to treat for both internists and surgeons alike. While a somewhat rare entity with a prevalence reported to be approximately between 1 and 3% among patients with renal failure [1–3], 3HPT nonetheless poses a complex problem which doctors have attempted to treat through both conservative and aggressive means. 3HPT most commonly arises in the setting of renal disease, as is often seen in secondary hyperparathyroidism (2HPT). However, 3HPT can be distinguished from 2HPT by persistent or recurrent hyperparathyroidism (HPT) after an initial period of stabilization even when the underlying renal disease is addressed, most often in the form of renal transplantation [4]. In fact, 3HPT has been observed in up to 30% of kidney transplant recipients [5]. It is important to note that renal failure is not the only context in which 3HPT can develop. Any abnormality that results in long-standing hypocalcemia, such as gastric malabsorption or chronic dialysis use, can cause 3HPT to develop. Essentially, 3HPT is the autonomous secretion of parathyroid hormone (PTH) by the parathyroid gland leading to persistent hypercalcemia and elevated serum PTH despite resolution of the underlying problem, most commonly treated by renal transplantation. Continuous stimulation of the parathyroid gland eventually causes it to become unresponsive to negative feedback mechanisms, and the parathyroid gland is often visibly and irreversibly enlarged with focal or diffuse nodularity.

3HPT can be detected through a clinical history of renal insufficiency in combination with high serum levels of PTH, calcium, phosphorus, and/or alkaline phosphatase levels around the time of renal transplantation [6,7]. Clinical presentations of 3HPT that warrant consideration of parathyroidectomy include fatigue, pruritus, bone pain, nontraumatic fracture, nephrocalcinosis, peptic ulcer disease [8,9].

Conservative medical management including calcimimetic agents [10,11] are usually first attempted before surgery is considered. Percutaneous ethanol injection therapy is an invasive measure that has been described recently [12–15] as a promising alternative, but the procedure is not without complications.

The indications for parathyroidectomy in patients with 3HPT are ill-defined as there are currently no evidence-based guidelines. Specifically, the role that serum calcium versus PTH levels play in defining operative indications is poorly described in literature. Particularly in patients that may not necessarily have both values of calcium and PTH levels elevated, questions remain regarding which value is more indicative of a need for parathyroidectomy. It follows that successful operations also have yet to be clearly delineated in terms of the primary outcome measures that are used to report cure rates.

In addition, the most appropriate surgical procedure, whether it be total, subtotal, or anything less than subtotal including “limited” or “focused” parathyroidectomies, continues to be unclear and controversial.

To date, there have been no systematic reviews investigating the role of parathyroidectomy in 3HPT. The aim of this study is to perform a thorough literature search in order to address the uncertainty surrounding the surgical indications, operative endpoint, differences in outcomes between varying extents of resection, efficacy in terms of cure and recurrence, and comparison between medical and surgical management for parathyroidectomy as an intervention for tertiary hyperparathyroidism.

## 2. Materials and methods

A systematic literature search of original articles using the PubMed, MEDLINE, and Cochrane Library databases was performed in accordance with PRISMA guidelines [16]. The most recent search was

conducted in June 2016 with the following search terms: (“tertiary hyperparathyroidism” OR “3HPT”) AND “parathyroidectomy”. Inclusion criteria were the following: (1) papers written in English, (2) primary studies with only human species, and (3) studies that characterized the efficacy of parathyroidectomy for tertiary hyperparathyroidism beyond the immediate post-operative period. Exclusion criteria were as follows: (1) narrative reviews or responses that did not analyze patient data, (2) case reports, (3) studies that did not report results specifically distinguishing patients with tertiary hyperparathyroidism from the rest of the study population, if any, and (4) studies that did not investigate in any form the efficacy of parathyroidectomy for tertiary hyperparathyroidism. Two reviewers identified articles based on inclusion and exclusion criteria. All articles that did not immediately meet exclusion criteria were individually reviewed in full text to confirm eligibility.

## 3. Results

Based on the search terms, a total of 206 papers were initially identified. After non-English and non-human studies were excluded, each of 158 papers were screened in detail. 24 narrative reviews and 42 case reports were excluded. 9 papers were excluded because the results were not specific to patients that had received parathyroidectomy for tertiary hyperparathyroidism. 53 papers were excluded because they did not quantify the efficacy of parathyroidectomy for 3HPT. Fig. 1 represents a flow chart of the article selection process.

Thirty studies met the criteria for inclusion. All but one study were retrospective analyses. One study [15] was a prospective review investigating outcomes in patients with 3HPT that were grouped into receiving percutaneous fine needle ethanol injection versus parathyroidectomy. Sample sizes of patients with 3HPT that underwent parathyroidectomy ranged from 5 to 140. 3HPT was defined as persistently high levels of parathyroid hormone, resulting in hypercalcemia despite correction of the underlying medical condition that previously caused hyperparathyroidism.

### 3.1. Surgical indications

Thirteen studies specifically delineated the indications they used to assess patients for parathyroidectomy. All studies required persistent hypercalcemia, whether symptomatic or asymptomatic, as one of at least two or more necessary criteria before considering surgery. The time point at which hypercalcemia was considered persistent varied but was most commonly defined as at least one year after renal transplantation. Values that qualified as hypercalcemia ranged from serum calcium levels >10 mg/dl to >11 mg/dl. Besides persistent hypercalcemia, most studies agreed that clinical manifestation of symptomatic hypercalcemia such as recurrent renal stones, severe arthralgia and myalgia, nephrocalcinosis, pruritus, calciphylaxis, renal osteopathy were criteria for surgical intervention. Of the studies that agreed that symptomatic hypercalcemia warranted surgical treatment, most accepted both specific and nonspecific signs and symptoms. Four studies [17–20] reported evidence of specific signs of hypercalcemia they required before operative consideration, and these are documented in Table 1. Only a few studies required an elevated serum PTH in addition to hypercalcemia in order to be considered [17,18,21–24].

### 3.2. Operative endpoint

The point during surgery at which the procedure for 3HPT patients was deemed successful was not detailed in every study. However, of

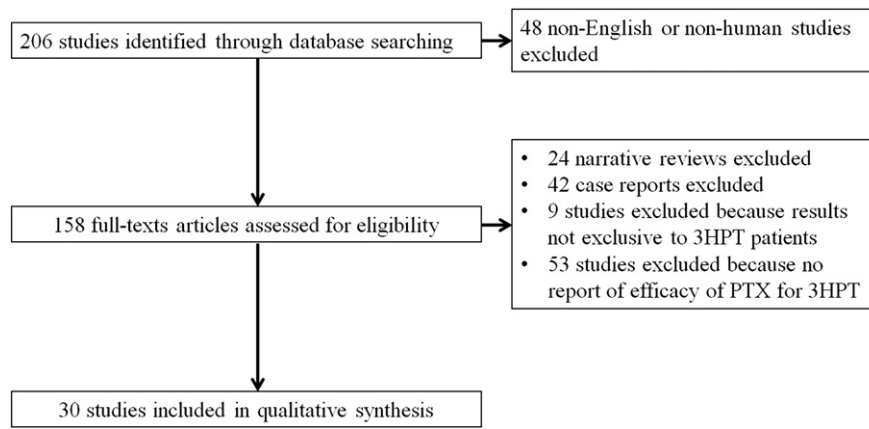


Fig. 1. Flow chart of article selection according to PRISMA guidelines.

the few studies that explicitly documented in their methods section the intraoperative endpoints they used to dictate completeness of surgery, all reported the criteria to end the operation as a decrease in intraoperative PTH >50% after resection [18,23,25–30]. All other studies either did not specify their operative endpoints, or simply discussed excision of abnormal appearing parathyroid tissue.

### 3.2.1. Comparison of extent of resection

Eleven studies compared outcomes between different surgical interventions. However, only five [17,19,21,31,32] directly compared subtotal versus total parathyroidectomy; most grouped subtotal and total parathyroidectomy together and even fewer compared “less than subtotal” to limited parathyroidectomy. Not all studies defined their procedures for subtotal parathyroidectomy, but for the most part, studies that performed subtotal parathyroidectomies defined these as removal of 3.5 glands [1,21,27,28,30,33–36]. Another common definition of subtotal parathyroidectomy involved leaving a remnant the size of two normal parathyroid glands behind [22–24,37], or leaving a remnant approximately 40–50 mg [18], 40–80 mg [29], or 30–50 mg [38] in size. Of the studies that compared total to subtotal parathyroidectomies,

three found no difference in recurrence rates between groups [21,32]. One study [31] found a significant correlation between extent of surgery and decline in serum calcium levels with more extensive resections exhibiting greater declines; however, these results were only consistent at 3- and 6-month postoperative follow-up and were no longer detected at 12 months. Another study [19] did not characterize success in terms of cure rates. Instead, the authors found significant worsening of renal graft function in total parathyroidectomies when compared to subtotal parathyroidectomies.

The majority of the studies that investigated the effects of different surgical interventions grouped subtotal and total parathyroidectomies into the same group and compared these to a “less than subtotal” or limited parathyroidectomy. In general, these were defined as removal of one or two parathyroid glands [1,22,34]. Among these, results were mixed regarding whether the more limited parathyroidectomy was associated with a higher recurrence rate [22,29] or showed no difference [1,3,34].

There was a trend toward a higher incidence of complications with greater extent of resection. Specifically, higher rates of transient hypocalcemia [1,19] or deterioration of graft function [17,19] were noted in the group of patients that underwent a more complete parathyroidectomy.

Table 1

Objective signs and symptoms of hypercalcemia as indication for parathyroidectomy in tertiary hyperparathyroidism.

Author (Year)	Article title	Indication for PTX in 3HPT
Ohe (2003)	Usefulness of a rapid immunometric assay for intraoperative parathyroid hormone measurements	<ul style="list-style-type: none"> <li>Intractable pruritus not responding to intensive dialysis or to other medical interventions</li> <li>Progressive extraskelatal calcifications</li> <li>Severe bone pain or fractures</li> <li>Development of calciophylaxis</li> </ul>
Schlosser (2007)	Surgical treatment of tertiary hyperparathyroidism: the choice of procedure matters!	<ul style="list-style-type: none"> <li>Nephrocalcinosis or stone formation of the renal graft</li> <li>Severe renal osteopathy</li> <li>Soft tissue calcification</li> <li>Pruritus</li> </ul>
Gasparri (2009)	The usefulness of preoperative dual-phase 99mTc MIBI-scintigraphy and IO-PTH assay in the treatment of secondary and tertiary hyperparathyroidism	<ul style="list-style-type: none"> <li>Aseptic necrosis of femoral head</li> <li>Tendon calcification</li> <li>Development of renal stones in grafted kidney</li> </ul>
Jager (2011)	Effect of incomplete parathyroidectomy preserving entire parathyroid glands on renal graft function	<ul style="list-style-type: none"> <li>Renal osteopathy</li> <li>Severe nephrocalcinosis within renal graft</li> <li>Pruritus and bluish skin lesions (as symptoms of calciophylaxis)</li> </ul>

PTX: parathyroidectomy; 3HPT: tertiary hyperthyroidism; IO-PTH: intraoperative parathyroid hormone.

### 3.2.2. Efficacy of parathyroidectomy: cure and recurrence of disease

All studies found that parathyroidectomy was an effective treatment for 3HPT to some degree. While the majority of the studies defined success rates as normocalcemia at follow-up, usually at 6 months after parathyroidectomy, the definition of “cure” is still rather vague and not clearly defined in all papers (Table 2). Only three studies required normal PTH levels in addition to normocalcemia at follow-up to be considered a successful parathyroidectomy [18,19,36]. Both preoperative and postoperative PTH levels were reported in most, but not all, studies and were not mandatory to define cure. In some cases, normocalcemia even with persistent PTH elevation after parathyroidectomy was still deemed to be a cure [33,39]. Two studies [22,29] reported two different cure rates in terms of both serum calcium levels and PTH levels. In both cases, the cure rates were much higher when they were defined by normocalcemia rather than PTH levels (94–100% cure defined by calcium levels, 70.6–76% cure defined by PTH levels). Some studies even documented resolution of preoperative symptoms as the most important consideration for success [3,35]. In total, cure rates were documented between 93 and 100% and recurrence rates ranged from 5 to 10% with long-term follow-up.

Two studies reported on the efficacy of parathyroidectomy by examining parameters related to renal function rather than normalization of serum calcium or PTH levels [19,40]. Kandil et al. [40] found that parathyroidectomy for 3HPT was associated with worsening glomerular filtration rate, but these results did not significantly decrease long term

**Table 2**  
Definitions of success after parathyroidectomy (PTX) for tertiary hyperparathyroidism (3HPT) as delineated by different studies.

Author (Year)	Article title	Definition of success after PTX for 3HPT
Lou (2016)	Parathyroidectomy is underused in patients with tertiary hyperparathyroidism after renal transplantation	• Normal serum calcium and normal PTH at 6 months postoperatively
Pitt (2010)	Secondary and tertiary hyperparathyroidism: the utility of ioPTH monitoring	• Normal serum calcium at 6 months postoperatively
Gasparri (2009)	The usefulness of preoperative dual-phase 99mTc MIBI-scintigraphy and IO-PTH assay in the treatment of secondary and tertiary hyperparathyroidism	• PTH < 65 pg/ml at 6 months postoperatively • Calcium < 10.5 mg/dl at 6 months postoperatively
Schlosser (2007)	Surgical treatment of tertiary hyperparathyroidism: the choice of procedure matters!	• Normal serum calcium and normal PTH at 6 months postoperatively
Abboud (2003)	Tertiary hyperparathyroidism in patients on hemodialysis for chronic renal failure: subtotal parathyroidectomy or conservative treatment?	• Normal serum calcium or complete resolution of significant improvement of preoperative symptoms
Kilgo (1998)	Tertiary hyperparathyroidism after renal transplantation: surgical strategy.	• Resolution of hypercalcemia or resolution of or significant improvement of preoperative symptoms
Demeure (1990)	Results of surgical treatment for hyperparathyroidism associated with renal disease	• Normal serum calcium at 6 months postoperatively

PTX: parathyroidectomy; 3HPT: tertiary hyperparathyroidism; IO-PTH: intraoperative parathyroid hormone.

graft survival. This finding was supported by another study that showed that parathyroidectomy for 3HPT was not associated with rejection [36]. Schlosser et al. [19] proposed that while parathyroidectomy can effectively treat 3HPT, it poses a risk of impairing graft function, especially in patients that present with poor renal function at the time of parathyroidectomy.

Collaud et al. also illustrated parathyroidectomies to be an efficient treatment of osteoporosis and osteopenia in patients with 3HPT by increasing bone mineral density [37].

### 3.2.3. Medical vs. surgical management

Three studies from the search term results compared parathyroidectomy to more conservative approaches. Parathyroidectomy was preferred to medical management with calcimimetic agents due to significantly greater reductions in serum calcium and PTH levels and lower incidence of persistent hypercalcemic symptoms [36,41]. Percutaneous fine needle ethanol injection as an alternative strategy to parathyroidectomy was also investigated, but it was ultimately concluded that its effectiveness is somewhat unpredictable and the long term results are poor compared to parathyroidectomy for 3HPT [15].

## 4. Discussion

While 3HPT is a disease that has been characterized for some time now, standard guidelines dictating optimal therapy remain elusive. In the ever-changing landscape of emerging technology and novel medical therapies, the ideal treatment plan for these patients continue to evolve. There is often no fault in attempting conservative management first. Calcimimetic agents have well-established benefits for treating 2HPT [42,43] largely because 2HPT patients present with hypocalcemia, but these agents are less studied for persistent hyperparathyroidism in the setting of renal failure such as is seen in 3HPT. Outcomes appear to be suboptimal [41] compared to parathyroidectomy for definitively treating 3HPT. Percutaneous ethanol injection therapy has also been

discussed recently, but does not demonstrate any advantage to parathyroidectomy [15,44]. Furthermore, the procedure is not without complications and has been reported to significantly complicate any subsequent surgery [15,45].

For those patients that continue to suffer from 3HPT despite optimal medical management, surgery is often the next step. Indications for surgery as well as a curative procedure are not clearly defined, especially regarding the role of PTH levels in assessing surgical candidacy and cure. The results of the systematic review suggest that persistent hypercalcemia after renal transplant as well as achievement of normocalcemia postoperatively is the most important value to take into account. Achieving normocalcemia postoperatively is so valuable largely because it is the high calcium levels that are the main driving force behind the numerous symptoms and clinical manifestations that plague these patients with 3HPT who have already failed medical therapy. Symptomatic hypercalcemia is loosely defined among the studies, and most include both specific and nonspecific signs and symptoms as sufficient to warrant parathyroidectomy. The few studies that necessitated quantifiable evidence specifically examined patients for signs of calciphylaxis such as intractable pruritus and bluish skin lesions and documented instances of aseptic necrosis of the femoral head, tendon calcifications, nontraumatic fractures, and nephrocalcinosis, or renal stones within the graft.

Although there is general agreement that hypercalcemia and its clinical manifestations, both vague and specific, are the most crucial elements to determine operative consideration and cure, results are mixed regarding whether to include elevated serum PTH in the analysis. Nevertheless, there seems to be a trending acceptance that elevated PTH in the setting of normocalcemia is insufficient indication for parathyroidectomy for 3HPT without other findings. This line of thought is consistent with endocrinology textbook definitions of surgical indication for tertiary hyperparathyroidism which suggest persistent hypercalcemia after 12 months of observation as the main indication without consideration of PTH levels [46]. Undoubtedly, biochemical mechanisms influencing serum PTH levels may be more complicated than mere inhibitory signals, and elevated PTH alone may not exhibit obvious symptoms as hypercalcemia often does. In more than one study [33,39], as many as 21–46% of patients had persistent elevated PTH after parathyroidectomy despite resolution of hypercalcemia and the authors concluded that this was likely a function of decreasing GFR, vitamin D deficiency, or the presence of a hyperplastic remnant without hypercalcemia. Evidently, vitamin D deficiency is the most common reason for secondary elevations of PTH in the setting of normocalcemia [47]. Furthermore, while 3HPT patients are usually hypercalcemic, their PTH levels are generally lower than those of 2HPT patients due to the ability of the kidneys to clear C-terminal PTH fragments [38]. While it may seem illogical to refuse operation in a patient with an extremely elevated PTH if their calcium levels are normal, it is an interesting question whether the scenario of elevated PTH to the thousands of pg/ml in the setting of normocalcemia even exists. On the other hand, it is very possible that because tertiary hyperparathyroidism by definition requires elevated PTH, some clinicians may not have documented this as an operative indication given the obvious necessity of “hyperparathyroidism” in the name of the disease. Regardless, it appears that most studies agree that normalization of PTH is not an essential metric of success in the same way that normocalcemia at follow-up represents success, so much so that not all studies reported postoperative PTH levels. This is a marked difference from the requirements of success in primary hyperparathyroidism which mandates normalization of PTH in addition to serum calcium levels.

Moreover, the operative endpoint for parathyroidectomy in 3HPT is not as well-defined as the widely accepted requirements to end the procedure in primary hyperparathyroidism patients. Nevertheless, the studies that have reported the specific measures they use to define operative endpoint utilize concur that a decrease in intraoperative PTH >50%, measured at least 10 min after resection was sufficient to

determine conclusion of surgery, even if PTH was still above normal. This is a crucial difference from the operative endpoint in parathyroidectomy for primary hyperparathyroidism in which both a normal PTH as well as a >50% drop in PTH levels are required before conclusion of surgery. It is somewhat unclear whether excision of abnormal appearing parathyroid tissue by itself is deemed an endpoint to surgery as some authors only report visual inspection of normal remaining glands prior to concluding surgery.

When the option of surgery is evaluated, the extent of resection of the parathyroid gland remains somewhat controversial. The type of surgical intervention, though, is often dictated by findings in the operating room. Most often, obvious nodularity and adenomas of the parathyroid gland are treated with a more focused approach while diffuse hyperplasia warrants a more complete resection [1]. Some institutions only performed “near total” or “subtotal” parathyroidectomies on all their patients [23,39]. Although the studies evaluated in the systematic review utilized different grouping schemes to compare the effect of surgical intervention on disease outcomes, there was a general consensus to recommend more limited resection due to similar “cure” rates with fewer complications. Furthermore, limited parathyroidectomies may ameliorate potential downstream consequences of more extensive surgeries. In fact, reduced renal function and graft deterioration have been observed more frequently in patients undergoing total parathyroidectomies [19,40]. Hypocalcemia, while transient in the postoperative period, is also more commonly seen following greater resections [1,19]. There were only a few studies that advocated for total parathyroidectomies in order to protect renal function and minimize disease recurrence [27,48].

Many factors influence the cure rates of 3HPT treated with parathyroidectomies. Preoperative imaging [8,18,49,50] as well as novel surgical adjuncts and techniques such as intraoperative PTH monitoring [8, 20,26,28,30,33,51] and radioguided parathyroidectomies [25,52,53] have been proposed to increase the likelihood of success, most likely through improving the accuracy of removing the diseased portions of the parathyroid gland.

As is inherent in all systematic reviews, the variability of reporting quality poses a limitation to readers in their ability to thoroughly assess the strengths and weaknesses of each study. Nevertheless, the explicit method by which the systematic review was conducted effectively minimizes bias. It is also important to note that most of the studies were retrospective reviews; therefore, patients who underwent parathyroidectomy already reached the limit of medical therapy and may have a different set of comorbidities apart from the entire group of patients with 3HPT. Prospective studies randomizing 3HPT patients to medical versus surgical management may be a future direction worth considering.

A particular strength of this study lies in its exclusivity in evaluating 3HPT. 2HPT and 3HPT are distinct disease entities and therefore warrants separate analyses. Consequently, studies that did not independently evaluate 3HPT were excluded. Indeed, quite a few studies were excluded despite demonstrating promising new information regarding outcomes, largely because there were no distinctions between patient groups that had 2HPT versus 3HPT [2,44,53–59]. Especially since the clinical question studied aims to highlight the efficacy of parathyroidectomy precisely in the context of 3HPT, only studies that reported results specifically for 3HPT patients would paint the most accurate portrait of success.

## 5. Conclusion

The findings of this review suggest that surgery, in the form of limited, subtotal or total parathyroidectomy, is a reasonable treatment option for tertiary hyperparathyroidism. While more studies recommended a more focused surgical approach, substantial evidence regarding complication rates are sparse. This study highlights key points in which surgery for 3HPT differs largely from surgery for primary

hyperparathyroidism. Unlike parathyroidectomy for primary hyperparathyroidism, hyperparathyroidism alone is not an indication for surgery without other findings; rather, increased PTH in conjunction with increased levels and symptoms of serum calcium is an indication. All patients undergoing parathyroidectomy for 3HPT must have already failed medical management before surgery is considered. Interestingly, despite the intuitive assumption that reducing PTH would be the primary goal of surgery, the operative endpoint of surgery is not necessarily a return of PTH to normal, but a >50% drop in PTH level even if PTH remains above normal. Additionally, “success” or “cure” is defined as normal calcium levels regardless of whether or not PTH is elevated. Based on studies reviewed, the goal of surgery for 3HPT is not a normal PTH value; instead, a normal calcium level at least six months postoperatively is the main objective.

Further prospective studies that investigate the long-term consequences of parathyroidectomies on renal function in patients with 3HPT are needed. A more comprehensive evaluation of the benefits and costs of medical versus surgical management would also certainly add the limited knowledge in literature regarding the role of parathyroidectomy as a potential cure for 3HPT.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Competing interests

The authors declare that they have no competing interests.

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Not applicable.

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