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Recent advances in the treatment of parathyroid disease

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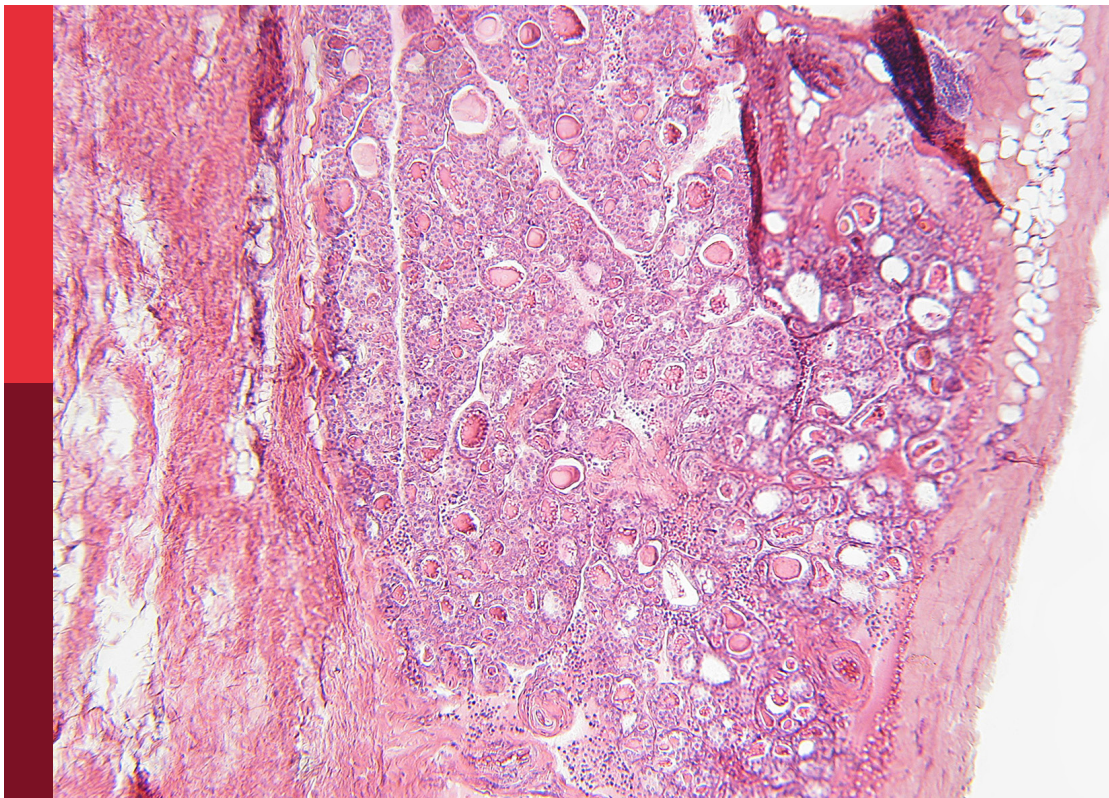

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Recent advances in the treatment of parathyroid disease

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Table of contents

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Editorial: Recent advances in the treatment of parathyroid disease

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Editorial on the Research Topic
Recent advances in the treatment of parathyroid disease

This Research Topic, "Recent Advances in the Treatment of Parathyroid Disease," focuses on various aspects of treatment of primary, secondary, and tertiary hyperparathyroidism. Additionally, it discusses techniques to preserve the parathyroid glands (PTGs) during thyroidectomy. Karwacka et al. demonstrated the effect of parathyroidectomy (PTx) for primary hyperparathyroidism (PHPT) on hypertension control and left ventricular function. After PTx for PHPT, 78% of patients showed improvement in hypertension (HT). Six months post-PTx for PHPT, improvements in left atrial and ventricular function in patients with HT were demonstrated using transthoracic echocardiography. This study investigated the association between PHPT and cardiovascular disease. Li et al. analyzed the literature on cinacalcet and secondary hyperparathyroidism (SHPT). According to this meta-analysis, cinacalcet reduced the serum parathyroid hormone (PTH), calcium, phosphate, and calcium-phosphate product levels. However, cinacalcet did not improve the all-cause or cardiovascular mortality rates. Although a significant reduction in the incidence of PTx was not observed, there was a tendency towards it in cinacalcet users. Adverse events such as nausea, vomiting, and hypocalcemia were significantly more frequent in cinacalcet users. This report suggests the importance of PTx in the treatment of SHPT despite the drastic reduction in PTx numbers following the development of cinacalcet. Hiramitsu et al. reported the treatment of SHPT, focusing on PTx. They were the first to demonstrate the operative indications of PTx for SHPT and also discuss an associated preoperative imaging evaluation method. They also discussed the advantages and disadvantages of each PTx surgical procedure for SHPT and concluded that total PTx with autotransplantation and transcervical thymectomy might be the best approach. Additionally, they highlighted the importance of intraoperative neuromonitoring, intact PTH monitoring, and frozen section diagnosis. They then described the diagnosis and repeat PTx of persistent and recurrent SHPT after PTx. Moreover, they discussed medical treatment for SHPT and compared treatment outcomes between calcimimetics and PTx. Hiramitsu et al. investigated predictive factors for autograft-dependent recurrent SHPT after total PTx. In their study, multivariate analysis demonstrated that dialysis vintage and the maximum diameter of the PTG for autografts were significant contributing factors to autograft-dependent recurrent

Abbreviations: HT, hypertension; IONM, intraoperative neural monitoring; PTGs, parathyroid glands; PTH, parathyroid hormone; PTx, parathyroidectomy; PHPT, primary hyperparathyroidism; RLN, recurrent laryngeal nerve; SHPT, secondary hyperparathyroidism; THPT, tertiary hyperparathyroidism.

SHPT after total PTx. Receiver operating characteristic curve analysis indicated that a PTG diameter <14 mm was optimal for autografts. Additionally, they explored the correlation between pathological findings (the hyperplastic pattern of PTG used for autografts) and autograft-dependent recurrent SHPT, though they did not identify a significant relationship between the hyperplastic pattern of the PTG used for the autografts and autograft-dependent recurrent SHPT. Based on these results, they concluded that a PTG <14 mm should be used as an autograft to prevent autograft-dependent recurrent SHPT. Casella et al. investigated surgical treatment for tertiary hyperparathyroidism (THPT). They compared the total PTx with autotransplantation to the subtotal PTx for THPT. Although the study included only a small number of patients, there were no significant differences in persistent or recurrent THPT, transitory hypocalcemia, or temporary or permanent hypoparathyroidism between the two operative procedures. Statistically, significantly lower mean calcium and intact PTH levels were observed among patients with total PTx in the autotransplantation group. However, the mean calcium and intact PTH levels were within the normal ranges. These results suggest that each operative procedure for THPT should be performed following an adequate patient-informed interview, preoperative multidisciplinary discussion, and consideration of intraoperative findings. Rao et al. reported preservation of PTGs during thyroid and neck surgery. They discussed the causes of postoperative hypocalcemia, including surgical factors related to preserving the PTGs. To preserve PTGs appropriately, they detailed the anatomy of PTGs and the techniques used to identify them. They described autofluorescence using infrared cameras and carbon nanoparticles as a preservation technique, as well as outlined procedures for autotransplantation. Wang et al. investigated preservation methods for PTGs using carbon nanoparticles during endoscopic thyroid cancer surgery. Carbon nanoparticles accumulate in the lymph nodes, staining the thyroid tissue and lymph nodes black. This enables surgeons to perform a thorough lymph node dissection in the central area. Additionally, the "negative parathyroid imaging effect" of the carbon nanoparticles allows surgeons to easily identify PTGS and safely preserve parathyroid function. Mu et al. investigated the impact of recurrent laryngeal nerve (RLN) monitoring on parathyroid surgery. While the effectiveness of intraoperative neural monitoring (IONM) in thyroid surgery is well-documented, its usefulness in parathyroid surgery, especially PHPT, remains to be investigated. In the present study, the incidence of transient RLN injury was significantly lower in patients who underwent PTx for PHPT with IONM. The results of this study verified the usefulness of IONM in PTx for PHPT. Recent advancements have been reported in the treatment of parathyroid disease. We anticipate that this series of articles will contribute to the continuing refinements of surgical interventions for parathyroid disease.

Author contributions

TH: Writing – original draft. ZM: Writing – review & editing. TA: Writing – review & editing.

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Treatment for secondary hyperparathyroidism focusing on parathyroidectomy

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Secondary hyperparathyroidism (SHPT) is a major problem for patients with chronic kidney disease and can cause many complications, including osteodystrophy, fractures, and cardiovascular diseases. Treatment for SHPT has changed radically with the advent of calcimimetics; however, parathyroidectomy (PTx) remains one of the most important treatments. For successful PTx, removing all parathyroid glands (PTGs) without complications is essential to prevent persistent or recurrent SHPT. Preoperative imaging studies for the localization of PTGs, such as ultrasonography, computed tomography, and ^{99m}Tc-Sestamibi scintigraphy, and intraoperative evaluation methods to confirm the removal of all PTGs, including, intraoperative intact parathyroid hormone monitoring and frozen section diagnosis, are useful. Functional and anatomical preservation of the recurrent laryngeal nerves can be confirmed *via* intraoperative nerve monitoring. Total or subtotal PTx with or without transcervical thymectomy and autotransplantation can also be performed. Appropriate operative methods for PTx should be selected according to the patients' need for kidney transplantation. In the case of persistent or recurrent SHPT after the initial PTx, localization of the causative PTGs with autotransplantation is challenging as causative PTGs can exist in the neck, mediastinum, or autotransplanted areas. Additionally, the efficacy and cost-effectiveness of calcimimetics and PTx are increasingly being discussed. In this review, medical and surgical treatments for SHPT are described.

KEYWORDS

secondary hyperparathyroidism, parathyroidectomy, chronic kidney disease, autotransplantation, mortality, calcimimetics

Abbreviations: CKD, chronic kidney disease; CT, computed tomography; FGF-23, fibroblast growth factor-23; IOIPTH, intraoperative intact parathyroid hormone; IONM, intraoperative neuromonitoring; KDIGO, Kidney Disease Improving Global Outcomes; ESRD, end-stage renal disease; KDOQI, National Kidney Foundation's Kidney Disease Outcomes Quality Initiative; MIBI, Sestamibi; PHPT, primary hyperparathyroidism; PTG, parathyroid gland; PTH, parathyroid hormone; PTx, parathyroidectomy; QOL, quality of life; RLN, recurrent laryngeal nerve; SHPT, secondary hyperparathyroidism; SPECT, single photon emission computed tomography; US, ultrasonography.

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1 Introduction

During the early stages of chronic kidney disease (CKD), serum fibroblast growth factor-23 (FGF-23) increases to prevent hyperphosphatemia. However, FGF-23 can significantly suppress the synthesis of activated vitamin D, 1α,25-dihydroxyvitamin D. As the CKD progresses, further decreases in activated vitamin D and increases in the serum phosphorus levels can cause hypocalcemia. Additionally, the decreased expression of the vitamin D and calcium-sensing receptors expressed on the parathyroid cells can worsen secondary hyperparathyroidism (SHPT) (1). Severe SHPT can occur during long-term treatment for end-stage renal disease (ESRD). Furthermore, the incidence of severe SHPT with intact parathyroid hormone (PTH) levels >300 pg/mL is estimated to be approximately 33% (2).

For the treatment of SHPT, phosphorus binders and vitamin D receptor activators were developed; however, they were ineffective in cases of severe SHPT (1). For those with severe SHPT, the parathyroid glands (PTGs) progress to nodular hyperplasia, in which vitamin D receptor expression is decreased (3, 4). Although phosphorus binders are useful to improve serum phosphate levels, they do not reduce serum PTH effectively (5). Therefore, parathyroidectomy (PTx) is the radical surgical treatment for severe SHPT. PTx helps to improve bone mineral density, bone fracture risk, patient survival, and quality of life (QOL) (6–10).

In addition to the medical and surgical treatments, interventional treatment such as ultrasound-guided percutaneous ethanol injection (PEIT) is indicated for patients with only one enlarged PTG with a volume of >0.5 cm^3 (11, 12). An advantage of interventional treatment is that it can be performed without general anesthesia and operation. In long-term ESRD conditions, patients with SHPT do not always tolerate general anesthesia and operation, and interventional regimens can therefore be a good treatment option (13–17). However, disadvantages include the risk of pain, hematoma, and recurrent laryngeal nerve (RLN) injury (12). The 66–85% success rate of PEIT is slightly lower than that of PTx, with persistence and recurrence rates of 5–30% (11, 18–22). Additionally, the number of patients indicated for interventional treatment is limited (11, 12). The mainstream SHPT treatment remains medical and surgical.

Recently, the development of calcimimetics has dramatically reduced the number of surgical treatments needed (23, 24). However, PTx for SHPT is still required considering its cost-effectiveness and application for drug-refractory SHPT (25–27). The difficulty of PTx for SHPT differs from PTx for primary hyperparathyroidism (PHPT) because complete removal of all PTGs is required to prevent persistent or recurrent SHPT (28). In PTx for PHPT, identification of PTGs is relatively easy (29), and causative PTGs are often identified during preoperative imaging studies (29). The Miami criteria for intraoperative intact parathyroid hormone (IOIPTH) monitoring have been established and are useful for confirming the resection of causative PTGs during PTx for PHPT (30). However, in PTx for SHPT, preoperative imaging studies can rarely identify all PTGs (20, 31), and criteria for IOIPTH monitoring have not been established. Additionally, PTGs firmly adhering to the RLNs are sometimes identified due to hemorrhage or calcification in the PTGs; thus, removing these PTGs may result in RLN injury (32).

When persistent or recurrent SHPT is suspected, localization of causative PTGs is required. However, when total PTx with autotransplantation is performed in the initial PTx, localization becomes particularly challenging as causative PTGs can occur in the autografted, cervical, or mediastinum areas (33). Additionally, the selection of timely and appropriate treatment requires an understanding of the differences between PTx and medical treatment with calcimimetics.

In recent years, considering the popularity and availability of calcimimetics, the rate of PTx has decreased, and it has become difficult for young surgeons to gain experience performing PTx for SHPT (23, 24). However, PTx remains an important treatment option for SHPT. In this review, the medical and surgical treatments for SHPT were comprehensively explained to serve as a reference for the next generation of surgeons and to improve patient outcomes (Figures 1, 2).

2 Indication for PTx

The Kidney Disease Improving Global Outcomes (KDIGO) 2009 and Japanese Society for Dialysis Therapy 2012 guidelines

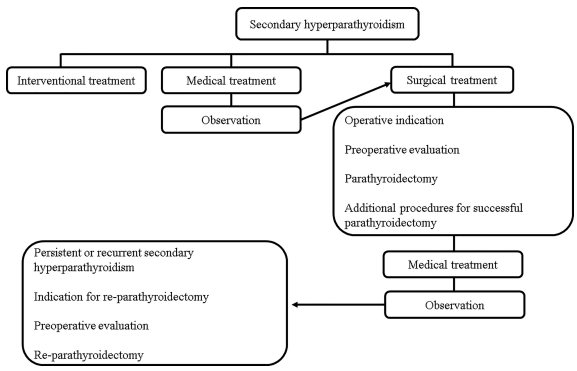

FIGURE 1
Flowchart of secondary hyperparathyroidism treatment.

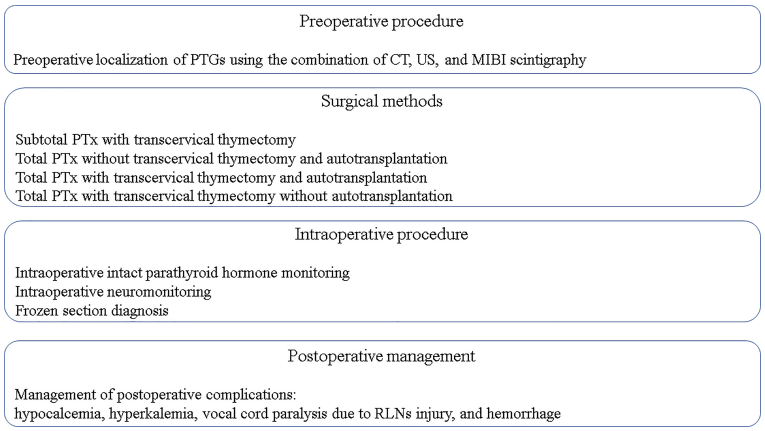

FIGURE 2
Key principles to achieve a successful PTx. CT, computed tomography; MIBI scintigraphy, ^{99m}Tc-Sestamibi scintigraphy; PTx, parathyroidectomy; PTGs, parathyroid glands; RLNs, recurrent laryngeal nerves; US, ultrasonography.

have defined the operative indications for SHPT (34, 35). In the KDIGO guidelines, the target range for intact PTH levels is within 2–9 times the upper normal range for patients with stage 5D CKD, equivalent to 130–600 pg/mL. When marked changes are identified in intact PTH levels, treatment initiation or a change in therapy is suggested. PTx is recommended when medical therapy has failed (34). In the Japanese Society for Dialysis Therapy 2012 guidelines, the target range for PTH is 60–240 pg/mL (35), and PTx is recommended when the intact PTH level is >500 pg/mL or whole PTH is >300 pg/mL (35, 36). Although the intact and whole PTH levels are lower than the suggested levels in hyperphosphatemia or hypercalcemia refractory to medical treatment, both conditions are indications for PTx. The target ranges for serum phosphorus and calcium are defined in the the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) 2003 and Japanese Society for Dialysis Therapy 2012 guidelines (35, 37). Additionally, subjective complaints related to SHPT, including high bone turnover, significant changes on radiography, and ectopic calcification, can be positive indications for PTx (35). In the KDIGO 2017 clinical practice guideline update, medical therapy using calcimimetics, calcitriol, or vitamin D analogs are additionally suggested as PTH-lowering therapy (38). However, PTx is still regarded as a "valid treatment option" when medical therapy has failed, as suggested in the KDIGO 2009 guideline (34, 38).

3 Preoperative imaging evaluations for PTx in SHPT

During PTx for SHPT, preoperative imaging evaluations of the swollen PTGs are essential to ensure complete removal. In SHPT, CKD stimulates all PTGs, which should be removed in the initial PTx. However, remnant PTGs are also stimulated and cause persistent or recurrent SHPT (28, 39). Re-PTx for persistent or recurrent SHPT increases the risk of RLN injury owing to PTG adhesion from the initial PTx (40, 41). However, it is sometimes difficult to identify supernumerary and ectopic PTGs, and even locating the four main PTGs, namely the right upper and lower PTGs and left upper and lower PTGs, intraoperatively can be challenging (31, 42, 43). Supernumerary and ectopic PTGs are frequently located around the upper neck area, in the carotid sheath, within the thyroid gland, in the mediastinum, and in the thymus (18, 19, 31). Moreover, the color and shape of PTGs are similar to those of adipose tissues and lymph nodes. These similarities and unexpected locations often result in the misidentification of PTGs and, ultimately, unsuccessful PTx (44).

To minimize misidentification, preoperative imaging studies are essential, including ultrasonography (US), computed tomography (CT), and ^{99m}Tc-Sestamibi (MIBI) scintigraphy (45). US is a cost-effective, non-invasive, and non-radiographic imaging test; however, it is difficult to identify ectopic PTGs in the mediastinum. Conversely, CT and MIBI scintigraphy are radiographic imaging tests. CT is useful to identify the four main and ectopic PTGs, although PTGs in the thymus and thyroid gland are rarely identified. MIBI scintigraphy is useful in identifying ectopic PTGs especially in the mediastinum and upper neck area, although diagnostic accuracy is low due to false positives and false negatives (20, 45). The diagnostic accuracy of these imaging studies has been investigated (20, 43, 46–49). US showed the highest sensitivity (91.5%) and MIBI scintigraphy had the lowest sensitivity (56.1%). The sensitivity of combined US and CT and combined US, CT, and MIBI scintigraphy had a sensitivity value of 95.0% and 95.4%, respectively (47). Additionally, in a meta-analysis, the sensitivity and specificity of the MIBI scintigraphy was 58% and 93%, respectively (48). However, evaluating the diagnostic accuracy is challenging because the definition of the removal of all PTGs is ambiguous in these studies. Moreover, the number of PTGs differs among patients (50).

In our previous study, the diagnostic accuracies of US, CT, and MIBI scintigraphy were investigated in patients with intact PTH levels of <9 pg/mL on postoperative day one, which was lower than the normal range and indicated the complete removal of the PTGs (20). The diagnostic accuracy for the usual four PTGs on US, CT, MIBI scintigraphy, combined US and CT, combined US and MIBI

scintigraphy, combined CT and MIBI scintigraphy, and combined US, CT, and MIBI scintigraphy were 57.3%, 60.0%, 42.7%, 73.0%, 65.8%, 66.1%, and 75.1%, respectively. Combining US, CT, and MIBI scintigraphy had the highest accuracy for locating PTGs before PTx (20). Nevertheless, the diagnostic accuracy for locating the usual four PTGs was only 75.1% because approximately 18% (247 out of 1332 PTGs) were ectopic. Additionally, approximately 90% (231 out of 247 PTGs) of these ectopic PTGs are located in the thymus, making identification *via* imaging modalities challenging, considering the low sensitivity of MIBI scintigraphy and that the CT density and US pattern of PTGs is similar to those of lymph nodes and adipose tissues (31). The diagnostic accuracy for ectopic PTGs on US, CT, MIBI scintigraphy, combined US and CT, combined US and MIBI scintigraphy, combined CT and MIBI scintigraphy, and combined US, CT, and MIBI scintigraphy were 36.7%, 47.8%, 30.0%, 60.0%, 48.9%, 57.8%, and 63.3%, respectively (31). While these results for ectopic PTGs were similar to the four main PTGs, the diagnostic accuracy for ectopic PTGs was somewhat lower. This implies that the identification of ectopic PTGs *via* preoperative imaging is more difficult than that of the usual PTGs (31).

Supernumerary PTGs also increase the difficulty of PTx. Approximately 6% of all resected PTGs (44 out of 747 PTGs or 90 out of 1422 PTGs) were supernumerary PTGs. None of the supernumerary PTGs were identified by US, CT, and MIBI scintigraphy. Notably, around 70% (64 out of 90 PTGs) were too small to be identified intraoperatively. These very small PTGs are referred to as micro nests and can only be identified by paraffin section diagnosis (31).

Persistent or recurrent SHPT can occur in 5–30% of patients, and re-PTx is required (18–21). The diagnostic accuracy of re-PTx has been investigated in a limited number of patients. The diagnostic accuracies of CT and MIBI scintigraphy were both 100%, although that of US was only 28% (31). Causative PTGs of persistent or recurrent SHPT are often located in the thymus and mediastinum; however, US cannot detect these because of the sternum and clavicle bones. In cases of re-PTx, preoperative CT and MIBI scintigraphy are thus required to localize the causative PTGs.

For the initial PTx, the accuracy of each imaging modality is not high. Therefore, for the precise preoperative localization of PTGs, combining US, CT, and MIBI scintigraphy is the favorable option where appropriate. Additionally, for re-PTx in the thymus and mediastinum, CT and MIBI scintigraphy are useful.

Recently, single photon emission computed tomography (SPECT/CT) has also been utilized for preoperative imaging evaluations. SPECT/CT is the fusion of CT and MIBI scintigraphy, which increases the localization accuracy of MIBI scintigraphy (43, 51, 52). For preoperative localization of PTGs, the findings of CT and US should be carefully evaluated prior to PTx.

4 Surgical procedure of PTx for SHPT

The surgical procedure can consist of a combination of total or subtotal PTx, transcervical thymectomy, and autograft. The following four procedures are often described in reports:

1. Subtotal PTx with transcervical thymectomy
2. Total PTx without transcervical thymectomy and autotransplantation
3. Total PTx with transcervical thymectomy and autotransplantation
4. Total PTx with transcervical thymectomy and without autotransplantation

In this section, the advantages and disadvantages of these surgical procedures are compared and reviewed. First, the frequency of these four procedures in previous reports was analyzed. Total PTx with transcervical thymectomy and autograft is the most common globally at 68.1%, followed by subtotal PTx with transcervical thymectomy at 19.8%, total PTx without transcervical thymectomy and autograft at 10.3%, and total PTx with transcervical thymectomy and without autograft at 1.6% (53).

Subtotal PTx with transcervical thymectomy involves removing 3.5 PTGs and leaving 40–80 mg of PTG tissue. PTGs with a normal appearance are favored for preservation to avoid recurrence. Transcervical thymectomy is usually added to prevent persistent and recurrent SHPT due to ectopic or supernumerary PTGs in the thymus. The frequency of ectopic and supernumerary PTGs in the thymus is 22.0–39.3% and 6.5–37%, respectively (19, 20, 49, 50, 54). The advantage of this procedure is that hypoparathyroidism can be avoided by leaving a PTG. However, there is a potential risk of direct dissemination to the surroundings and hematogenous dissemination to other organs from the PTG stump (55). Persistent or recurrent SHPT due to dissemination makes it almost impossible to remove causative disseminated PTGs (55), whereas persistent and recurrent SHPT due to the remaining PTG requires re-PTx.

Total PTx without transcervical thymectomy and autograft is performed to prevent hypoparathyroidism after PTx as PTH secretion is expected from the ectopic and supernumerary PTGs in the thymus. One disadvantage is the potential risk of recurrent or persistent SHPT due to the remnant PTGs in the thymus, which increases the risk of RLN injury in the case of re-PTx (56). The causative PTGs in the thymus in persistent or recurrent SHPT are comparatively close to the RLNs. For safe re-PTx, intraoperative neuromonitoring (IONM) is recommended because of adhesion due to the initial PTx (57). Another disadvantage is that general anesthesia is essential in the case of re-PTx. Patients with severe SHPT often experience other complications such as cardiovascular diseases and cervical destructive spondyloarthropathy owing to long-term CKD (13–17). These complications can cause unstable vital signs during general anesthesia and cervical spine injury during intubation or surgical positioning. Furthermore, there is a potential risk of postoperative bleeding as a result of the dissection of adhesions and fragile tissues associated with CKD. Postoperative bleeding can narrow the trachea and potentiate the risk of suffocation. Therefore, re-PTx should be avoided in patients with SHPT. However, subtotal PTx with transcervical thymectomy and total PTx without transcervical thymectomy and autograft are selected for patients expecting kidney transplantation in the near future as improved kidney function after transplantation does not stimulate the remnant PTGs; therefore, persistent or recurrent

SHPT can be avoided (58). Additionally, although improved kidney function can cause hypoparathyroidism, the PTH secreted from remnant PTGs can avoid this problem (59).

Total PTx with transcervical thymectomy and autograft is the most common procedure globally (53). The risk of persistent or recurrent SHPT in the neck can be almost entirely prevented after successful PTx. Moreover, hypoparathyroidism is prevented by the expected secretion of PTH from the autograft (60). This procedure is favored in both patients expecting long-term dialysis and those expecting kidney transplantation (61). The most common location for the autograft is the forearm since removal of the recurrent PTGs can easily be performed under local anesthesia. However, the diagnosis of causative PTGs in persistent or recurrent SHPT is complicated. The neck and mediastinum areas and forearm are distinct locations which cannot be examined simultaneously. Methods to locate causative PTGs are reviewed in Section 6.

Total PTx with transcervical thymectomy without autograft is rarely performed due to the complete lack of PTH secretion (53). The impact of hypoparathyroidism after PTx has also not been fully revealed (62). In the KDIGO 2009 guidelines, this procedure was contraindicated for patients expecting kidney transplantation because hypoparathyroidism after transplantation may cause serious bone metabolism problems and hypocalcemia (34).

5 Comparison of PTx procedures

5.1 Subtotal PTx versus total PTx with autotransplantation

Literature comparing surgical procedures for SHPT is limited. Complications, reoperations, readmission, and 30-day mortality were similar between subtotal and total PTx with autotransplantation in a report based on data from the American Surgical College of Surgeons National Surgical Quality Improving Program (63). This study demonstrated similar short-term outcomes for both PTx procedures. Additionally, in a randomized trial, significant improvements in clinical signs and calcium levels were observed, and re-PTx was not identified in the total PTx with autotransplantation group. This study demonstrated the superiority of total PTx with autotransplantation compared to subtotal PTx (64).

In a retrospective study by the Swedish Renal Registry, long-term outcomes were investigated (65), and the risk of cardiovascular events was lower in subtotal than in total PTx. This can be explained by the lower PTH levels in total than in subtotal PTx, although 78% of patients underwent autotransplantation after total PTx. Low bone turnover due to low PTH levels can increase the calcification of coronary arteries (66, 67). The re-PTx rate is higher in subtotal than in total PTx due to the low kidney transplantation rate in this group (65), although previous reports demonstrated similar re-PTx rates for subtotal and total PTx (68). Rates of hip fracture, paralysis of RLNs, and mortality are similar between subtotal and total PTx (65). Furthermore, in a systematic review on the prevention of SHPT after subtotal or total PTx with autotransplantation, symptomatic improvement, radiological change, hypocalcemia rate, persistence rate, time to recurrence, recurrence rate, and reoperation rates were similar (69).

The QOL between subtotal and total PTX with bilateral cervical thymectomy and autotransplantation was investigated using the 36-item Short Form Health Survey questionnaire (6). In this prospective randomized trial, there were no significant differences in QOL between procedures for SPHT. The study concluded that PTx can improve the QOL of patients with SHPT regardless of the surgical procedure.

These studies imply that total PTx is favored for patients who need long-term dialysis, although special attention is necessary for cardiovascular events. However, subtotal PTx can be indicated for patients with SHPT expecting kidney transplantation in the near future (70, 71).

5.2 Total PTx without autotransplantation versus total PTx with autotransplantation and transcervical thymectomy

In most of the literature regarding total PTx with autotransplantation, transcervical thymectomy was performed. Regarding the short-term outcomes investigated in a multicenter prospective randomized controlled pilot trial, paralysis of RLNs, postoperative bleeding, and postoperative hypocalcemia were similar in both total PTx without autotransplantation and total PTx with autotransplantation and transcervical thymectomy. Moreover, mortality after 3 years of follow-up was also similar (72). However, PTH levels were significantly higher at the end of follow-up after PTx with autotransplantation and transcervical thymectomy.

In a systematic review involving 1108 patients across 11 studies, symptomatic improvement, surgical complications such as postoperative bleeding, RLN paralysis, and all-cause mortality were similar for both procedures. Re-PTx owing to persistent or recurrent SHPT was performed more frequently in total PTx with autotransplantation and transcervical thymectomy (73). Hypocalcemia was more frequently identified in total PTx without autotransplantation, although hypoparathyroidism was similar between the two surgical procedures. Similarly, in a meta-analysis including 1283 patients across 10 studies, persistent or recurrent SHPT occurred more frequently after total PTx with autotransplantation and transcervical thymectomy. However, hypoparathyroidism often develops after total PTx without autotransplantation, although permanent hypocalcemia and adynamic bone disease were not reported (60). These studies demonstrated similar short- and long-term outcomes for both procedures, except for the higher rate of re-PTx for persistent or recurrent SHPT in total PTx with autotransplantation and transcervical thymectomy.

It should be noted that in these studies the locations of causative PTGs were not revealed in total PTx with autotransplantation and

transcervical thymectomy. If causative PTGs in the neck or mediastinum can be identified more frequently in total PTx with autotransplantation and transcervical thymectomy, the success rate of PTx should be improved, reducing persistent or recurrent SHPT. In this case, the impact of both procedures on persistent or recurrent SHPT cannot be compared. When initial PTx is successful, persistent or recurrent SHPT is caused by the transplanted autograft and appropriate PTGs for the autograft should be discussed in more detail. PTGs with nodular hyperplasia more frequently cause recurrent SHPT than diffuse glands (74). Previous reports suggested that PTGs with a maximum diameter >8 mm on preoperative US can indicate nodular hyperplastic changes (75). This implies that PTGs for autografts should be fragmented from PTGs with a maximum diameter <8 mm on preoperative US. However, the intraoperative characteristics of appropriate PTGs to prevent recurrent SHPT have not been investigated, although the relationships between intraoperative parameters and pathological patterns have been reported (76, 77).

5.3 Subtotal PTx versus total PTx without autotransplantation versus total PTx with autotransplantation and transcervical thymectomy

Only one systematic review comparing the above three surgical procedures was identified (78). This systematic review included 5063 patients across 26 reports (78). Hypocalcemia and hypoparathyroidism were most frequently identified in total PTx without autotransplantation, whereas the frequency was similar in subtotal PTx and total PTx with autotransplantation and transcervical thymectomy. Persistent or recurrent SHPT and re-PTx were most common in subtotal PTx. Based on these results, total PTx with autotransplantation and transcervical thymectomy was recommended for SHPT.

This comparison implies that subtotal PTx is not appropriate for patients who require long-term dialysis owing to the high incidence of persistent or recurrent SHPT caused by the remaining PTGs. In contrast, patients who require kidney transplantation can be indicated for subtotal PTx. However, the impact of hypoparathyroidism after total PTx without autotransplantation on bone metabolism, cardiovascular events, and mortality in the long term (e.g., 10 years) has not been reported. Patients who undergo total PTx without autotransplantation may experience hypoparathyroidism and hypocalcemia after kidney transplantation. Thus, avoiding total PTx without autotransplantation is preferred for optimal patient outcomes.

At present, total PTx with autotransplantation and transcervical thymectomy is the best option for SHPT. The rate of persistent or recurrent SHPT originating from PTGs in the neck or mediastinum area is low. Recurrent SHPT caused by the autograft can easily be addressed by the removal of the causative PTGs under local anesthesia. The appropriate PTx procedure should be selected based on the patient's condition and the schedule for kidney transplantation.

6 Additional methods during PTx

Additional measurements to ensure successful PTx, including IONM, IOIPTH monitoring, frozen section diagnosis, and other methods are reviewed in this section.

6.1 IONM

Proper identification of PTGs and the presence of RLNs contribute to the difficulty of PTx. Identification of RLNs is essential during PTx to prevent RLN injury, which can lead to hoarseness and difficulty in swallowing and breathing. IONM was developed to prevent RLN injuries. Electronic stimulation of the RLNs causes movements of the vocal cord, detected by the attachment around the tracheal tube (79). This response to IONM implies anatomical and functional preservation of the RLNs.

The diagnostic accuracy of IONM in the initial PTx is 94.7%, suggesting that a positive or negative IONM response during PTx can predict intact vocal cord movement or vocal cord paralysis in 94.7% of RLNs (32). Although the diagnostic accuracy of IONM during PTx is high, preserving the RLNs is difficult in some cases. Inflammation due to calcification and hemorrhage of the PTGs can cause severe adhesion of the PTGs to the RLNs (80). In these cases, accurate dissection is required, and IONM should be indicated. In cases with severe adhesion of the PTGs to the RLNs, IONM allows the incidence of vocal cord paralysis to be lowered to a similar incidence as without severe adhesion (32). Predictive factors for severe adhesion of the PTGs to the RLNs are a maximum diameter >15 mm, weight >500 mg, and nodular hyperplasia. Based on these parameters, IONM should be indicated when PTGs with a maximum diameter >15 mm are identified on preoperative imaging.

Although IONM is a useful method in PTx, the accuracy is not 100%. This might be due to false-positive cases in which a positive IONM response did not lead to intact vocal cord movement, possibly caused by delayed neuropraxia due to edema or laryngeal edema. Additionally, false-negative cases where intact vocal cord movement was identified despite a negative IONM response may be caused by malpositioning of the tracheal tube or temporary intraoperative RLN paralysis (79). These issues should be considered when using IONM.

6.2 IOIPTH monitoring

Intraoperative PTH monitoring was first developed to ensure the removal of causative PTGs in PHPT (30, 81–83). Preoperative PTH levels and PTH levels after the removal of causative PTGs are measured to investigate the appropriate decrease in PTH levels for predicting successful PTx. In PTx for PHPT, a 50% decrease 10 minutes after the removal of causative PTGs was demonstrated as the best indicator of successful PTx (30). Similarly, researchers have tried to adapt intraoperative PTH monitoring for PTx for SHPT. However, the condition of patients with SHPT is different from that of patients with PHPT. The kidney function of most patients with

PHPT is within the normal range, whereas patients with SHPT have ESRD, which makes it difficult to establish criteria for intraoperative PTH monitoring.

PTH is a single-chain polypeptide hormone consisting of 84 amino acids (84). Whole PTH, referred to as 1-84 PTH, is biologically active and metabolized into multiple fragments in the liver and kidneys (85). Although whole PTH should be measured during intraoperative PTH monitoring, the widely available second-generation intact PTH assay kit that uses an enzyme-linked immunosorbent assay with a one-step sandwich method is problematic as cross-reactivity between 7-84 PTH and whole PTH causes a discrepancy between measured intact PTH and whole PTH levels, especially in patients with ESRD (86, 87). In healthy populations, the 7-84 PTH fragment is mainly excreted in the urine, and the impact of cross-reactivity is low. In patients with ESRD, the pharmacological half-life of 7-84 PTH is several hours owing to poor kidney function, whereas the pharmacological half-life of whole PTH is approximately 3–4 minutes. Although intraoperative PTH monitoring is expected to obtain results within 10–20 minutes during the operation, the discrepancy of the half-lives and cross-reactivity between 7-84 PTH and whole PTH make it difficult to establish the criteria for IOIPTH monitoring to predict successful PTx.

Additionally, establishment of IOIPTH monitoring criteria for the prediction of successful PTx requires reputable operative methods and techniques. In recent studies, these criteria were investigated (31, 88, 89). We previously showed that a 70% decrease in intact PTH 10 minutes after total PTx and transcervical thymectomy can predict successful PTx, defined as an intact PTH level <60 pg/mL on postoperative day one (88). This was considered to be the definition of successful PTx because the incidence of re-PTx for recurrent or persistent SHPT was significantly lower in patients with an intact PTH level <60 pg/mL on postoperative day one (31, 88). The accuracy of this criterion was 92.9%. Among 226 patients, 26 benefited from IOIPTH monitoring. In five patients, IOIPTH did not decrease >70%, and further exploration was needed to remove the additional PTGs. In 21 patients, although fewer than four PTGs were removed, IOIPTH decreased by >70%, indicating that the operation was complete, avoiding potential RLN injury. The limitation of this criterion is its low specificity (52.2%). This is caused by patients in whom IOIPTH decreased by >70% but intact PTH on postoperative day one was >60 pg/mL, indicating the existence of residual PTGs despite the decrease in IOIPTH. Subsequently, these criteria were further investigated by Zhang et al. (89). Total PTx without thymectomy was performed, and the definition of successful PTx was intact PTH <50 pg/mL 1 week after PTx. The criterion for successful PTx was a >88.9% decrease in IOIPTH 20 minutes after total PTx without thymectomy, with a positive predictive value of 97.1% and a negative predictive value of 26.5%.

Following these studies, despite the different surgical procedures and definitions of successful PTx, the appropriate criteria for IOIPTH monitoring during PTx for SHPT were established. These IOIPTH criteria may help ensure successful PTx. Recently, a third-generation PTH assay has become available (90), in which whole PTH can be measured without cross-reactivity with 7-84 PTH. However, as intraoperative PTH monitoring during PTx for SHPT has not been investigated using this assay, appropriate criteria for successful PTx remain to be elucidated.

6.3 Frozen section diagnosis

The importance of frozen section diagnosis has rarely been investigated (31); however, the significance might depend on the availability of pathologists. In our previous study, IOIPTH monitoring and frozen section diagnosis were independent contributing factors to successful PTx (31, 91). The importance of IOIPTH is discussed in Section 6.2. In terms of frozen section diagnosis, the number of PTGs identified was a significant contributing factor according to the multivariate logistic regression analysis (31). Additionally, the diagnostic accuracies of frozen section and surgeons for PTGs were investigated by comparison with paraffin section diagnosis. Frozen section diagnosis had a higher diagnostic accuracy than surgeons at 99.4% and 88.9%, respectively. This implies that the diagnosis of PTGs by surgeons is not sufficient. Thyroid glands, lymph nodes, and adipose tissue were misdiagnosed by surgeons as PTGs, and the causes of these misdiagnoses were investigated. Notably, PTGs mimic the appearance of surrounding tissues, making it difficult for surgeons to distinguish them from the surrounding tissues. Moreover, although misdiagnosis using frozen sections is rare, thyroid glands and lymph nodes were misdiagnosed as PTGs. As mentioned in this study, using IOIPTH monitoring simultaneously improves the success of PTx as 6.6% of all resected PTGs, consisting of 4.9% supernumerary PTGs and 1.7% usual four PTGs, were not identified by frozen section diagnosis (31). To confirm the resection of these PTGs, IOIPTH monitoring is useful.

Additionally, in cases of total PTx and autograft for SHPT, the selection of PTGs for autograft is important. To avoid hypoparathyroidism and autografting lymph nodes or thyroid tissues involved in thyroid cancer, frozen section diagnosis is required. However, frozen section diagnosis should be performed by experienced pathologists. When PTx for SHPT is required and experienced pathologists are not available, patients should be referred to hospitals with experienced surgeons and pathologists.

6.4 Other methods

Radio-guided PTx is reported to be useful in identifying PTGs intraoperatively. In radio-guided PTx, preoperative MIBI is administered intravenously, and MIBI-accumulated PTGs are detected by the gamma counter. Radio-guided PTx for SHPT has been reported to be useful in identifying ectopic and undetected PTGs (92).

Recently, near-infrared autofluorescence imaging has been developed to identify PTGs without using a radio-active substance. Instead, this method uses the unique autofluorescent signature of PTGs under near-infrared wavelengths (93). The usefulness in clinical practice has been demonstrated (94–96). Currently, the only method to confirm the complete removal of

PTGs during surgery is IOIPTH monitoring; however, near-infrared autofluorescence imaging has the potential to locate ectopic PTGs and those with a similar appearance to surrounding tissues. Nevertheless, the suitability of near-infrared autofluorescence imaging in PTx for SHPT remains to be investigated in large-scale studies (97–99).

Frozen section diagnosis is the most reliable method for confirmation of PTGs during surgery. However, parathyroid aspiration in which PTH levels in the resected PTGs are measured and used for the confirmation of PTGs is an alternative method with high sensitivity (100–102). The efficacy and cost-effectiveness of parathyroid aspiration should be further investigated with large trials. However, considering the cost-effectiveness, frozen section diagnosis may be replaced with parathyroid aspiration in the future after establishing its efficacy.

Overall, these additional methods, along with IONM, IOIPTH monitoring, and frozen section diagnosis, may be advantageous for PTx for SHPT. In particular, IONM is an indispensable method in thyroid and parathyroid surgeries as RLN injury can significantly deteriorate patient QOL. Further research with large-scale randomized trials is needed to fully elucidate the risks and benefits of each of these modalities, alone and in combination, for PTx in SHPT.

7 Postoperative complications and treatments

Postoperative complications include hypocalcemia, hyperkalemia, vocal cord paralysis due to RLNs injury, and hemorrhage. Following the significant decrease in PTH after PTx, marked skeletal uptake of calcium occurs and leads to hypocalcemia, named "hungry bone syndrome," in which prominent bones form after PTx (103). Hypocalcemia is identified in 27% of patients on dialysis (61). Hypocalcemia can cause symptoms such as muscle cramps, tingling in the lips, tongue, fingers, and feet, and positive Chvostek or Trousseau sign. To prevent hypocalcemia, calcium replacement therapy is essential after PTx to maintain adequate serum calcium levels (37, 104, 105). After PTx for SHPT, "the blood level of ionized calcium should be measured every 4 to 6 hours for the first 48 to 72 hours after surgery and then twice daily until stable" according to KDOQI clinical practice guidelines for bone metabolism and disease in CKD (37).

Additionally, severe hyperkalemia is identified in 6.3% of patients after PTx for SHPT in a report of 1500 cases (106). In the case of postoperative severe hyperkalemia, urgent dialysis is required to prevent cardiovascular events. The risk factors of hyperkalemia after PTx for SHPT are not well demonstrated, although the relationships of hyperkalemia with gender, age, obesity, and preoperative serum potassium levels are mentioned in small-sized studies (107–109).

Postoperative hemorrhage is a serious complication leading to suffocation. Meticulous hemostasis is essential in preventing postoperative hemorrhage; however, postoperative hemorrhage can occur in 0.07–5% patients after thyroid and parathyroid surgery (110, 111). To reduce the compression to the trachea in case of postoperative hemorrhage, opening the wound without delay is the first and most important procedure. After securing the airway by endotracheal intubation or tracheostomy, reoperation under general anesthesia should be considered (110, 111).

Vocal cord paralysis due to RLNs injury is also a serious complication. In PTx for SHPT, RLN injury was identified in 2.47% cases in a report of 1500 cases (106). The prevention of RLN injury using IONM is essential, as discussed in Section 6.1.

8 Persistent or recurrent SHPT after PTx

8.1 Diagnosis of persistent or recurrent SHPT

The management of SHPT after PTx is not meticulously detailed in the clinical guidelines. For the follow-up of parathyroid function, serum PTH levels should be measured every 3 months in CKD stage 5 patients as mentioned in the KDOQI clinical practice guidelines for bone metabolism and disease in CKD (37). Similarly, persistent or recurrent SHPT has also not been defined in the guidelines. In previous reports, the definition of persistent or recurrent SHPT is usually based on the target serum intact PTH levels in the KDIGO guidelines 2009 or Japanese Society for Dialysis Therapy 2012 guidelines, with a target range of 2–9 times the upper normal range, equivalent to 130–600 pg/mL or 60–240 pg/mL, respectively (34, 35). Persistent SHPT is defined in some reports as serum intact PTH levels that do not decrease beyond the lower limit of the target range after PTx (28, 31, 33, 39, 88). In contrast, serum intact PTH level increasing above the upper limit should be defined as recurrent SHPT. However, the operative indication of initial PTx for SHPT with serum intact PTH levels >800 pg/mL in the KDOQI clinical practice guidelines for bone metabolism and disease in CKD or >500 pg/mL in Japanese Society for Dialysis Therapy 2012 guidelines is used for indication of re-PTx for persistent or recurrent SHPT (35, 37). Moreover, these intact PTH levels are used as a definition of recurrent SHPT in some reports (31, 88, 112).

Persistent or recurrent SHPT may stem from the neck, mediastinum, or autografted forearm (33). In total PTx, the incidence of persistent or recurrent SHPT in the cervical area or mediastinum is 5–30% (18–21). The incidence of recurrent SHPT in the autografted forearm is 5%, although the number of related reports is limited (113). Persistent or recurrent SHPT more frequently requires re-PTx instead of medical treatment as most cases are refractory to medical treatment (28, 37). Before re-PTx, the preoperative localization of causative PTGs is essential. In the case of total or subtotal PTx without autograft, only the neck and mediastinum need to be investigated for causative PTGs. In contrast, when autograft is performed, localization of causative PTGs is more complicated as both the neck or mediastinum and the autografted forearm are potential sites.

Although localization is performed using US, CT, MIBI scintigraphy, or magnetic resonance imaging, it is not cost-effective to simultaneously evaluate both the neck or mediastinum and the autografted forearm. Before performing these imaging studies, we need to infer the approximate site of the causative PTGs. The Casanova test or modified Casanova test was developed for this purpose (114, 115). By measuring the blood levels of PTH from the bilateral forearm and the autografted arm and comparing the ratio, localization of causative PTGs can be inferred. However, the number of enrolled patients in these studies was limited, and avascularization with a tourniquet or Esmarch bandage for >10 minutes is required. Thus, we developed a new criterion to reduce the burden on patients (33); the duration of avascularization was only 5 minutes to determine the cutoff ratio of intact PTH levels for the diagnosis of causative PTGs. The intact PTH ratio (intact PTH level obtained from the non-autografted forearm/intact PTH level obtained from the autografted forearm) was significantly lower in patients with causative PTGs in the autografted forearm than in those in the neck or mediastinum. Furthermore, receiver operating characteristic curve analyses revealed the appropriate cutoff ratio for localization. An intact PTH ratio <0.310 indicated localization in the autografted forearm; an intact PTH ratio >0.859 indicated localization in the neck or mediastinum. However, an intact PTH ratio between 0.310 and 0.859 indicated that both areas need to be examined. Using this algorithm for the localization of causative PTGs can facilitate the diagnosis and decrease procedural costs.

In addition to conventional methods like palpation, magnetic resonance imaging is useful for the diagnosis of causative PTGs in the forearm (116). For diagnosis in the neck or mediastinum, the diagnostic accuracy of US is reportedly only 28.6% compared with 100% for CT and MIBI scintigraphy (20). However, it should be noted that in that study 57.1% (4 out of 7) of causative PTGs were in the intrathymic lesion or mediastinum, and US could not detect these PTGs owing to the clavicles or sternum. Recently, SPECT/CT imaging has been introduced to replace CT and MIBI scintigraphy for the detection of PTGs. Nonetheless, the usefulness of SPECT/CT imaging for the diagnosis of persistent or recurrent SHPT still needs to be investigated (117).

Although postoperative management and operative indications of persistent or recurrent SHPT after PTx is not currently established in any guidelines, the present indication for initial PTx for SHPT can be applied for the indication for re-PTx. Localization of causative PTGs can be roughly predicted using the Casanova test, modified Casanova test, or intact PTH ratio. For a detailed investigation, US and MRI are useful for causative PTGs in the forearm; CT and MIBI scintigraphy, or SPECT/CT imaging are useful for causative PTGs in the neck or mediastinum.

8.2 Re-PTx for persistent or recurrent SHPT

The indication for re-PTx for persistent or recurrent SHPT is the same as that for initial PTx (34, 35). Two kinds of operations are expected: re-PTx in the neck or mediastinum and re-PTx in the autografted forearm. Re-PTx in the neck can be performed from the same incision as the initial PTx. However, adhesion due to the initial PTx potentiates the risk of RLN injuries and postoperative hemorrhage (56). To prevent RLN injuries, precise preoperative localization of causative PTGs is essential. The usefulness of IONM was demonstrated in patients with re-operation for thyroid tumors (40). However, to the best of our knowledge, there are no studies evaluating the usefulness of IONM for re-PTx. Adhesion of PTGs to RLNs might occur after initial PTx, making it difficult to identify the RLNs. These situations can often be identified during re-PTx, and IONM should be applied for re-PTx cases. Re-PTx for cases of causative PTGs in the mediastinum requires sternotomy or thoracoscopic surgery. These procedures should be performed by experienced endocrine or thoracic surgeons. In addition, IOIPTH monitoring may be useful to confirm the removal of the causative PTGs; however, this has not been investigated to date.

PTG autografting involves the grafting of small, fragmented pieces of PTG under the skin or in the muscle. Re-PTx in the autografted forearm can be performed under local anesthesia. However, persistent SHPT can occur after re-PTx. To prevent persistent SHPT, the autografted PTGs need to be removed to the greatest extent possible. PTGs autografted in the muscle should be removed with the surrounding muscles to prevent very small remnant PTGs. Even after the removal of autografted PTGs, hypoparathyroidism rarely occurs (104). However, investigations on autograft after PTx such as operative methods, risk factors for recurrent SHPT, and repeated recurrent SHPT are still needed (74).

Studies describing the results after re-PTx are limited. Serum calcium levels have been demonstrated to decrease markedly from 10.2 mg/dL to 8.9 mg/dL after re-PTx, although the postoperative serum phosphorus levels were similar to preoperative levels (33). The patient survival rate after re-PTx has not been investigated. However, previous studies have demonstrated an increased mortality in ESRD patients with serum intact PTH levels > 400–600 pg/mL, implying that the re-PTx may improve mortality (118–122).

9 Outcomes of calcimimetics treatment and PTx

9.1 Cinacalcet hydrochloride

Cinacalcet was the first commercially available calcimimetic. Cinacalcet suppresses PTH production by allosterically attaching to the calcium-sensing receptors on PTGs (123). The MBD-5D study in Japan demonstrated a significant decrease in serum PTH and a favorable control of serum calcium and phosphorus by using cinacalcet with a reduced dose of a vitamin D agent (124). The direct effect of cinacalcet on PTGs has been demonstrated. Cinacalcet may cause histological changes and reduce the volume of enlarged PTGs (125, 126). The effect of cinacalcet on the bone was histologically demonstrated in the BONAFIDE study. In patients with high-turnover bone disease, long-term cinacalcet administration could improve the bone formation rate, bone metabolism markers, and histological findings (127). In the EVOLVE trial, cinacalcet treatment could significantly decrease

the incidence of clinical fractures as a secondary endpoint in the prespecified lag-censoring analysis compared with placebo, although statistical significance was not demonstrated in the intention-to-treat analysis (128). Additionally, improvements in mortality and cardiovascular events as the primary endpoint were demonstrated in the cinacalcet treatment group by the prespecified lag-censoring analysis compared with a placebo group, although a significant difference was not demonstrated in the intention-to-treat analysis (129). In the sub-analysis of the EVOLVE trial, the incidence of non-arteriosclerotic cardiovascular events such as sudden death and heart failure significantly decreased in the cinacalcet treatment group, although the incidence of arteriosclerotic cardiovascular events was not significantly different between the groups (130). In contrast, in the ADVANCE study, cardiovascular calcification was significantly prevented in the group receiving low-dose vitamin D sterols and cinacalcet compared with the low-dose vitamin D sterols treatment group (131). In studies in Japan and Australia, cinacalcet treatment improved all-cause mortality and mortality due to cardiovascular events (132, 133). Additionally, anemia was improved by cinacalcet treatment (134). While these beneficial effects were demonstrated, frequent gastrointestinal adverse events such as nausea and vomiting were also reported. Moreover, the probability of the ineffectiveness of cinacalcet due to non-adherence to the medication regimen has been discussed (129, 131, 135).

9.2 Etelcalcetide hydrochloride

Following the development of cinacalcet, etelcalcetide hydrochloride, which can be administered intravenously, was developed. In a randomized double-blind double-dummy clinical trial performed in the United States, Canada, European countries, Russia, and New Zealand, the effectiveness of etelcalcetide hydrochloride compared with cinacalcet was investigated. Etelcalcetide hydrochloride and cinacalcet similarly resulted in a >30% decrease in the serum PTH level; however, etelcalcetide hydrochloride was superior in achieving a >50% decrease in serum PTH (136). Etelcalcetide hydrochloride was also able to decrease FGF-23 more effectively than cinacalcet (137). In patients who were refractory to cinacalcet treatment due to poor compliance, SHPT was successfully managed with etelcalcetide hydrochloride (138). However, the frequency of gastrointestinal adverse events caused by etelcalcetide hydrochloride was almost equal to that of cinacalcet (137).

9.3 Evocalcet

The third calcimimetic is evocalcet, which can be administered orally. Evocalcet was developed to reduce the gastrointestinal adverse events associated with cinacalcet and etelcalcetide hydrochloride. In a head-to-head analysis, the completion rate to control intact PTH levels within the target range with evocalcet treatment was not inferior to that with cinacalcet. Additionally, the frequency of gastrointestinal adverse events was significantly lower at 18.6% in the evocalcet group compared with 32.8% in the cinacalcet group (139). Further, the effect of evocalcet on the improvement of FGF-23, serum-adjusted calcium, phosphorus, and bone turnover marker levels was similar to that of cinacalcet (139). Additional studies on the clinical outcomes of evocalcet are expected. The safety and efficacy after conversion from cinacalcet to evocalcet and after the long-term administration of evocalcet are expected to be demonstrated in the future (140).

9.4 PTx

The most radical and effective treatment for SHPT is PTx. Recently, SHPT refractory to medical treatment has been treated with PTx as a final treatment option. PTH levels dramatically improve after PTx, although calcium and vitamin D administration is indispensable owing to hypocalcemia. The improvement in bone density and the low frequency of bone fracture after PTx were demonstrated in an analysis of data from the United States Renal Data System (9, 141). A propensity score matching analysis of all-cause mortality and cardiovascular-related mortality demonstrated a 34% and 41% additional decrease in the PTx group compared with the non-PTx group for patients with severe SHPT, respectively (7). Similarly, in the PTx group, the all-cause mortality was superior to that in the non-PTx group according to the propensity score matching analysis of the United States Renal Data System data (8). Additionally, the effects of PTx in improving anemia, insomnia, cognitive status, peripheral arterial disease, and blood pressure have been demonstrated (142–146). The cost-effectiveness of PTx compared with medical treatment in patients eligible for PTx was also demonstrated (2, 37). As for the safety of PTx, the mortality rate within 30 days after PTx was only 2.0–3.1% (8, 147).

9.5 Calcimimetics treatment versus PTx

The importance of PTx after the development of calcimimetics needs to be discussed, as calcimimetics have dramatically reduced the need for PTx for SHPT. A direct comparison of the improvement in all-cause mortality between calcimimetics and PTx has not yet been reported. However, in a meta-analysis comparing medical treatment involving calcimimetics and PTx, the all-cause mortality and cardiovascular event-related mortality showed greater improvements in patients treated with PTx (148, 149). Moreover, in a prospective cohort study from Japan, PTx-treated patients were compared with matched cinacalcet-treated patients, and PTx reduced the risk of mortality, most prominently in patients with intact PTH levels ≥500 pg/mL and those with serum calcium levels ≥10 mg/dL (2). A recent study of the United States Renal Data System and Japanese Society for Dialysis Therapy Renal Data Registry also showed superior 5-year and 6-year survival in the PTx-treated group compared with the cinacalcet-treated group (2, 150). Additionally, from the viewpoint of QOL, the superiority of PTx compared with cinacalcet was demonstrated in a systematic review, where the physical component score and

mental component score in the 36-item Medical Outcomes Study Short-Form Health Survey were significantly more improved in the PTx-treated patients than in the cinacalcet-treated patients (151). Furthermore, PTx is more cost-effective than cinacalcet treatment (26, 27).

Although the number of PTx for SHPT has dramatically decreased after the various developments of calcimimetics, the advantages of PTx should be re-evaluated. PTx can be indicated for several patients, for example, young patients and patients with good general conditions who need long-term dialysis and medical treatment. Further studies on the indication of medical treatment or PTx should be investigated.

10 Discussion

The development of medical treatments including calcimimetics has changed the treatment of SHPT (23, 24). With the demonstration of efficacy, treatment for SHPT has changed from PTx to medical treatment. Nevertheless, patients with SHPT refractory to medical treatment exist (25). For these patients, PTx is the best treatment and should be indicated without delay to improve their QOL and reduce mortality (2, 150, 151). However, as the number of PTx for SHPT has decreased, consequently endocrine surgeons who have sufficient experience in performing PTx for SHPT are also decreasing. The difficulty of PTx for SHPT lies in removing all PTGs to prevent persistent or recurrent SHPT. For this purpose, preoperative imaging diagnosis and other intraoperative procedures are critical. Additionally, the appropriate PTx procedure should be selected according to the patients' condition and their schedule of kidney transplantation (53). Although there are several reviews on PTx for SHPT, there is no specific focus on the procedures for successful PTx, only on the outcomes after PTx. In this review, we focused on methods to achieve successful PTx based on previously published literature. Young endocrine surgeons might only have limited opportunities to perform PTx for SHPT. It is important to select the appropriate methods and modalities to ensure the success of PTx, and these principles should be handed down to the next generations. For such young endocrine surgeons, the authors hope that this review will be valuable. Considering that currently a limited number of studies have compared the safety and efficacy of calcimimetics and PTx, there is need for future studies to guide surgeons in choosing the optimal treatment approach. Moreover, future studies should investigate new modalities and methods to further improve the outcomes of treatment for SHPT.

Author contributions

TH drafted the manuscript. YH, KF, MO, NG, YT, SN, YW, and TI revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Preservation of parathyroid glands during thyroid and neck surgery

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The parathyroid glands are situated in close proximity to the thyroid gland. They have an important endocrine function maintaining calcium and phosphate homeostasis in the body by the secretion of parathormone (PTH), which is responsible for this function. The parathyroid glands are commonly damaged during thyroid surgeries. This could lead to transient or permanent hypoparathyroidism in 30% of cases. Preservation of the parathyroid glands, is an important and integral part of thyroidectomy and other surgical interventions in the neck. The main principle underlying this is a thorough understanding of parathyroid anatomy in relation to the thyroid gland and other important structures in the area. There can also be significant variation in the anatomical location of the glands. Various techniques and methods have been described for parathyroid preservation. They include intraoperative identification utilizing indocyanine green (ICG) fluorescence, carbon nanoparticles, loupes, and microscopes. The techniques of surgery (meticulous capsular dissection), expertise, central compartment neck dissection, preoperative vitamin D deficiency, extent and type of thyroidectomy are the risk factors associated with damaged thyroids, inadvertent parathyroidectomy and subsequent hypoparathyroidism. Parathyroid Autotransplantation is a treatment option for inadvertent parathyroidectomy. Ultimately, the best way to assure normal parathyroid function is to preserve them *in situ* intraoperatively undamaged.

KEYWORDS

Parathyroid identification, total thyroidectomy, hypocalcaemia, autotransplant, neck dissection

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Introduction

Surgery of the neck encompasses a wide variety of procedures of varying magnitude. Thyroidectomy is one of the most common procedures for benign disease, whereas neck dissection, is an integral component of malignant disease in the head and neck area. Morbidity associated with neck surgery include bleeding, lymphatic injury, nerve injury, and hypocalcaemia due to hypoparathyroidism. Post-surgical hypocalcaemia can be transient or permanent. Symptoms though transient can be significantly debilitating. Numbness, cramps, tetany, and confusion may require intravenous or multiple doses of calcium. Loss of vascularity can cause transient hypocalcaemia while inadvertent parathyroidectomy will cause permanent hypocalcaemia. Transient hypocalcaemia accounts for up to 18-30% and permanent is restricted to less than 3% of all thyroidectomies. Both transient symptomatic and permanent hypocalcaemia require treatment with permanent hypocalcaemia requiring lifelong oral calcium and active vitamin D3 supplements. Long-term complications include basal ganglia calcifications, renal calcification, carpopedal spasm, cardiac issues, and psychiatric problems (1). 75% of patients with permanent hypoparathyroidism experience significant symptomatology despite treatment and may require admissions. Autotransplant of the parathyroid gland is a reasonable treatment option to prevent permanent hypocalcaemia. There is however unpredictable viability and functionality of the transplanted parathyroid tissue in not an insignificant number of patients (2, 3). Lahey et al. (4) described the first parathyroid autotransplant and Wells published the first series of autotransplants (5). Parathyroid tissue for transplantation can be fresh or cryopreserved. Intraoperative preservations of parathyroid however remains the gold standard to ensure absence of postoperative hypoparathyroidism. Assessment of vascularity in the parathyroid by color assessment is subjective, hence the use of adjuncts to identify the gland (6, 7). Various methods have been found to identify and preserve these glands during surgery. The aim of this paper is to discuss the problem of postsurgical hypocalcaemia and synthesize the available surgical techniques, adjuncts and technological advances in preserving parathyroid function during neck surgery.

Post-operative hypocalcaemia: the magnitude of the problem

Hypocalcemia features in every discussion on the complications of thyroidectomy. While clinical features can range from the subtle (excessive fatigue, etc.) to the dramatic (stridor, seizures), it is clinically occult in the majority of patients with only biochemical evidence of hypocalcemia and sub-normal S. PTH levels.

Post-operative hypocalcaemia can be immediate, delayed, transient or permanent (Table 1).

It is generally transient and patients mostly recover within a few days after surgery. Various researchers have reported the incidence of transient post-thyroidectomy hypocalcemia between 2% & 51% (8–10). Transient hypocalcemia is seen so frequently after total thyroidectomy that it is now considered a sequel to the procedure and is no longer considered a complication (1). Permanent hypocalcemia as mentioned earlier is rare (0-3.6%) and can be managed with long term calcium and vitamin D replacement (11, 12). Renal failure, basal ganglia calcifications, neuropsychiatric derangements and infections are some of the complications of permanent hypocalcaemia which can have significant morbidity having a negative impact on daily living and quality of life in a subset of patients.

TABLE 1 Nomenclature of post-op hypocalcemia.

Immediate hypocalcemia	Presentation within 24hrs of surgery
Delayed hypocalcemia	Presentation after 24 hours after surgery
Transient hypocalcemia	Return of normocalcemia within 6 months of surgery
Permanent hypoparathyroidism	Persistent hypocalcemia and hypoparathyroidism for longer than 6 months post-op

Risk factors for post-operative hypocalcaemia

It is natural to ascribe post-operative complications to surgeon factors, but as a matter of fact, factors that put the patient at risk can be classified into surgical, anatomical, pathological and even metabolic factors that are independent of surgical anatomy or technique (Table 2).

Surgeon factors include tissue handling and dissection (capsular dissection, Figure 1), bleeding in the surgical field, use of magnifying aids like loupes and identification of the parathyroid glands on table (13). With the advent of newer surgical approaches with magnification and endoscopic assistance, we are beginning to see the effect of these aids on parathyroid preservation. There have been reports of significant reduction in post-op hypocalcemia with minimal access thyroidectomy (14).

The arterial twigs supplying the glands are end arteries with no collateral anastomoses. Even with the anatomy intact, these vessels might go into spasm post-operatively. Research has revealed that patients with normal S. iPTH levels (intact PTH in circulation) at the end of surgery can develop subnormal levels after surgery (15).

Various researchers have successfully correlated hypocalcemia with the number of parathyroids identified and preserved at surgery. Vidyasagar, et al. (15) estimated the intra-operative and post-operative iPTH levels and correlated these with the number of parathyroid glands which were devascularized or removed during total thyroidectomy. All those patients who had two or more viable and functional glands had normal levels of iPTH, with no significant difference between the intra-operative iPTH levels among them. In those patients with three devascularized glands, the iPTH levels were subnormal, while iPTH was undetectable after devascularization of four parathyroids. In a similar study, Rafferty, et al. (16) correlated post-op hypocalcemia with number of glands found in the specimen after thyroidectomy. The finding of 3 or

TABLE 2 Factors that influence post-operative hypocalcaemia.

Surgical	Rough tissue handling	Hinders identification
	Intra-operative angiospasm	Protective
	Bleeding in the surgical field	Protective
	Capsular dissection	Protective
	Energy devices	Protective
	Magnification (loupes, etc.)	Inferior glands especially at risk
	Endoscopic surgery	
	Two or more glands visualised and preserved	
	Inadvertent parathyroidectomy of two or more glands	
	Recurrent goitre	
	Lymph node dissection for cancer	
Anatomical	Anomalous location	
	End arteries	
Metabolic	Graves' disease and thyrotoxicosis	Hungry bone syndrome
	Macrodilution	
	General anaesthesia	
	Hypomagnesemia	
	Hypothermia	

more parathyroid glands in the specimen correlated with an incidence of 100% for post-operative hypocalcemia, while the incidence rate was 18% or less when two or fewer parathyroid glands were found on the specimen. Histopathological examination of the operated specimen confirms inadvertent parathyroidectomy. When evaluated so, the incidence of unintentional parathyroidectomy ranges from 9% to 19% in different series (17, 18).

Recurrent goitre and revision thyroidectomy is also associated with an increased risk of transient and permanent postoperative hypoparathyroidism (18, 19).

Risk of post-operative hypoparathyroidism and hypocalcaemia is increased in thyroid carcinoma and the procedure of lymph node dissection that may be necessitated (19, 20). Moley and de Benedetti (21) reported that adequate central node dissection is usually associated with compromise of the anatomy and/or blood supply of the parathyroid glands, especially the inferior parathyroids.

In addition to anatomical and surgical reasons, there are other metabolic factors which influence the development of post-operative hypoparathyroidism and hypocalcaemia. Thyroid hormones stimulate osteoclasts and calcium resorption. Post-operative hungry bone syndrome is well-recognised in thyrotoxicosis (17, 22, 23). Hypocalcemia has been shown to occur after other surgeries such as herniorrhaphy as well (22). Macrodilution of the intravascular fluid compartment, general anaesthesia, hypomagnesemia and hypothermia are some of the metabolic factors that might influence post-operative calcium levels (24, 25). With regards to gender, it has been found that this problem seems to affect the females more than males. It is thought that this is because the hormonal response of parathyroids is weaker in females than males (26, 27).

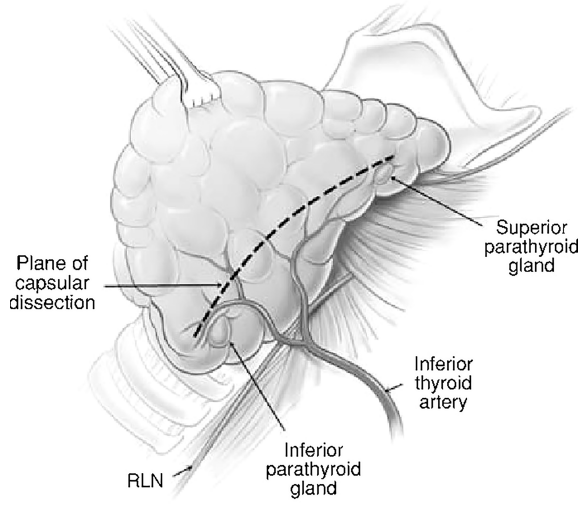

FIGURE 1
Capsular dissection: the line on the anterolateral surface of thyroid capsule along which dissection should proceed in order to preserve the parathyroids along with their blood supply.

Parathyroid anatomy: number and location

In an individual, there are usually 4 parathyroid glands which are situated adjacent to the thyroid gland. There is however significant developmental variation in the position of these glands. Historically, Richard Owen identified parathyroid in rhinoceros and Ivar Sandstrom named it 'glandulae parathyroidae' (28). The superior parathyroid glands are more anatomically consistent while the inferior parathyroid glands are more variable in position. Embryologically, the inferior parathyroid migrates to a greater extent hence, can be located anywhere between the hyoid bone and the superior mediastinum. This is the reason for the damage of parathyroid most often during surgical procedures in the central compartment of the neck (28, 29). Arterial supply to both superior and inferior parathyroid glands is predominantly from the inferior thyroid artery although there supply sometimes can arise from the superior thyroid artery and the thyroidea ima artery.

Classification of inferior parathyroid glands

A variety of classifications for the inferior parathyroid glands have been described in the literature.

Grisoli (Figure 2) classified the inferior parathyroid according to its relationship with the thymus (28–30).

Group 1 - parathyroid supplied by inferior thyroid artery behind and below the lower lobe of the thyroid

Group 2 - inferior parathyroid in the thyrothymic position placed midway between inferior thyroid lobe and cornua of the thymus

Group 3 - superior thymic parathyroid placed and the cornua of the thymus

Group 4 - intrathymic parathyroid

Based on the relationship between the blood supply of the thyroid and parathyroid, they are classified as follows: Type A- parathyroid supply independent of the thyroid with retained color after thyroidectomy, B1- parathyroid which retains partial blood supply from thyroid and sustains after removal of the thyroid, B2- parathyroid which retains partial blood supply from thyroid and is de-vascularized on the removal of the thyroid, B3- blood supply majorly from the thyroid, difficult to preserve *in situ* C- blood supply completely from the thyroid (30) Figure 3.

3. Based on the relationship between thyroid and inferior parathyroid by Zhu, 2 types- A- close contact, B- nonclose contact, A1-planar attachment, A2-embedded attachment, A3-intrathyroidal, B1-around thyroid, B2- intrathymic, B3- supply from thymus and mediastinum Figure 4.

While these classifications provide anatomic and surgical clues to the variations in parathyroid locations, there are also certain particular locations where they commonly reside.

- Around a 1cm circular area around the lower cornu of the thyroid cartilage, 85% of superior parathyroids lie here.
- In relation to the recurrent laryngeal nerve (% sign)- superior parathyroids are always posterior to the thyroid while inferior parathyroids anterior to the recurrent laryngeal nerve
- Related to the posterior and lateral surface of the thyroid

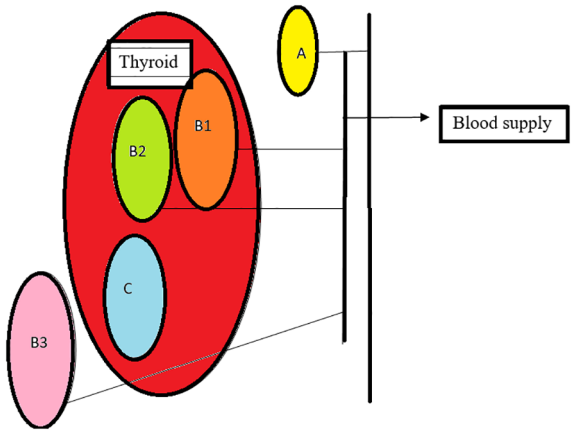

FIGURE 3
Types of parathyroid: **(A)**- non attachment to thyroid with adequate supply, **(B1)**- light attachment to thyroid with retained supply after thyroid removal, **(B2)**-light attachment to thyroid, changes color, needs auto graft, **(B3)**- blood supply from the thyroid, **(C)**- intracapsular, requires auto transplant.

Intraoperative characteristics which identify the parathyroid glands

1. A normal parathyroid gland measures 4-6mm with a maximum diameter of no more than 8mm
2. It is surrounded by a capsule with fat around the capsule
3. The parathyroid has a characteristic yellowish brown or tan brown color
4. It is softer than a lymph node
5. The parathyroids become pale when devascularized and congested on venous injury
6. It has a smooth and regular surface (29)

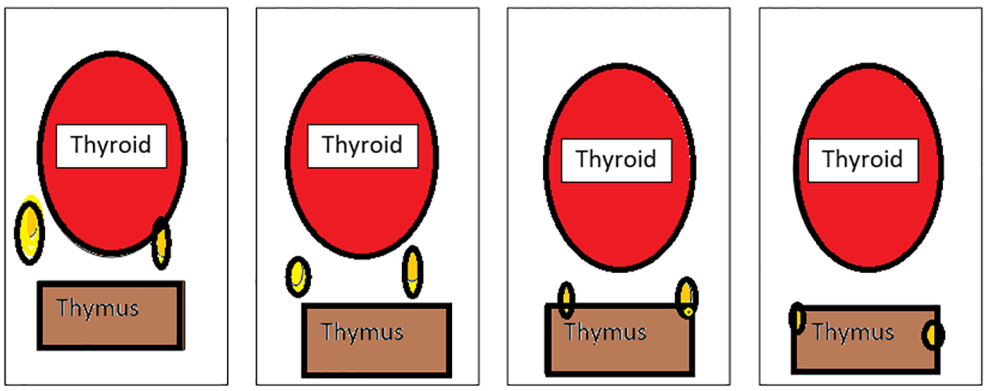

FIGURE 2
Types of inferior parathyroid (Grisoli)-(1): Usual, (2):Thyrothymic, (3): Superior thymic, (4): Intrathymic.

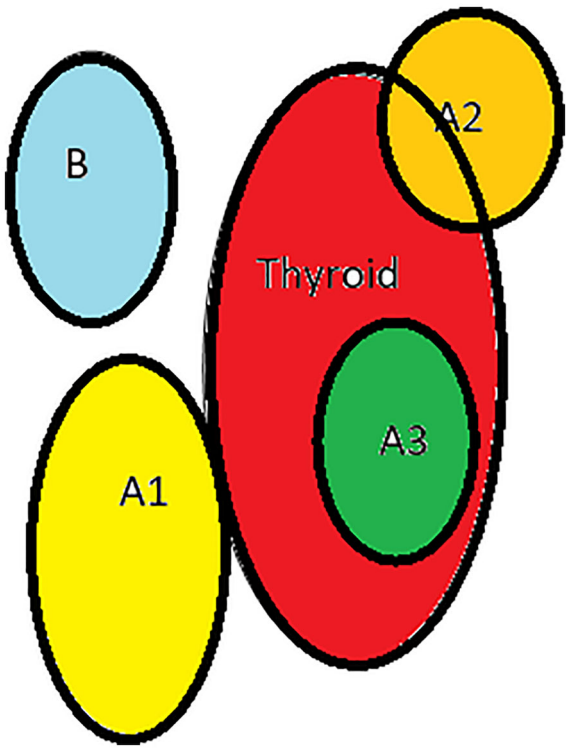

FIGURE 4
Types of inferior parathyroid (Zhu): **(A1)**-planar attachment, **(A2)**-embedded, **(A3)**- intrathyroid, **(B)**-non close contact.

Techniques to identify and preserve the parathyroid glands

Capsular dissection

Historically, the approach to thyroid surgery was to identify the recurrent laryngeal nerve early all along its length and remove tissue medial to the gland while attempting to preserve parathyroid blood supply, The issues with this approach were that the parathyroid glands were at risk of devascularization and the recurrent laryngeal nerve was also at risk due to the extensive dissection (2, 31). 'Capsular dissection' technique (Figure 1) in thyroid surgery is considered safe to preserve the recurrent laryngeal nerve and parathyroids and involves commencing the lateral dissection high on the thyroid gland dividing only the tertiary branches of the inferior thyroid artery. This safe ligation of the vascular supply close to the thyroid lobe is a way of preserving the blood supply of the parathyroid glands.

Routine vs. selective identification of parathyroid glands

Conventional thyroid and central neck surgery mandates the routine identification of every parathyroid gland during the operation. Several studies have suggested that the risk of hypocalcaemia increases when less than 2 parathyroid glands are identified during surgery. However, routine identification poses several risks including- inadvertent damage to the vascularity during dissection, non-identification of the gland due to its absence in the orthotopic position, and increased surgical time spent in finding the glands (32). Functionality of auto-transplanted glands of dubious *in situ* viability has been questionable (33–35). Some recent studies have, however, showed that identification of greater number of parathyroid glands during surgery increased the risk of post-operative hypocalcaemia. This led several surgeons to adopt a selective approach of only looking for parathyroid glands in orthoptic positions along with a capsular dissection technique which should further protect the parathyroid glands from damage (36, 37). Selective identification preserves vascularity and also saves surgical time (1). However, the quality of studies, low overall incidence of permanent hypocalcaemia, and conflicting evidence available in the literature make it very difficult to draw any concrete recommendation about the choice of approach. A detailed anatomical knowledge and subjective assessment will help in the intraoperative preservation of parathyroids. Endocrine surgeons have been known to be particularly trained to understand the viability of the glands in situ (28). Presence of supernumerary glands should also be kept in mind while looking for parathyroids, the characteristics of which have been described above (33). Symptomatic permanent hypocalcaemia is uncommon if at least one viable parathyroid is retained (38). The use of magnification loupes of two and a half times can be of useful to identify the recurrent laryngeal nerve, the parathyroids, and vascular anatomy, however it does not replace meticulous dissection (39). An important technique is the careful dissection, skeletonization of the stem of the inferior thyroid artery, hence preserving parathyroid vasculature. Intraoperative testing includes immersing a part of the parathyroid in saline to see whether it sinks/floats or having frozen section analysis (40). The tubercle of Zuckerkandl acts as a pointer with the superior parathyroids superior to the tubercle and inferior parathyroids inferior to it (41). 'Pinch, burn, and cut' is another technique on the thyroid capsule to safeguard the nerve and the parathyroid (42–44).

Inferior parathyroid gland preservation in central compartment lymph node dissection (CCLND)

A layer of TBP (Thymus, blood vessels and parathyroids) (Xie): Thymus, blood vessels, and parathyroids are all arranged in one layer (Figure 5). This layer is connected to the layer covering the common carotid, innominate artery, and paratracheal nodes (28).

Embryologically, the thymus as well as the inferior parthyroid glands comes from the 3rd pharyngeal pouch. Both of them migrate toward the superior mediastinum as the fetus grows. The thymic sheath is connected to the thyroid by the thyrothymic ligament which forms the basis of the layer of TBP.

During central compartment neck dissection, the layer of TBP forms the lateral margin of the dissection. The area from Berry's ligament to the thymus or brachiocephalic vessels forms the medial margin. The inferior thyroid artery is superficial to the TBP layer anterior to the common carotid artery. Hence, the layer of TBP,

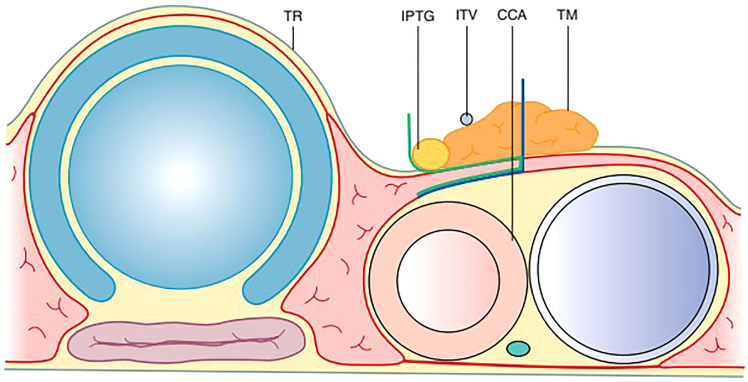

FIGURE 5
The TBP concept: Anatomy around the inferior pole of the thyroid lobe – Thymus, Blood vessel (inferior thyroid vein) and Parathyroid.

common carotid, and the recurrent laryngeal nerve are retracted laterally during the dissection of paratracheal nodes above and below the inferior thyroid artery. This concept of dissection led to significant improvement in the preservation of parathyroid *in situ* from 36 to 76% (Figure 6) (45, 46). Meticulous capsular dissection is another way to ensure parathyroid safety in situ.

Energy dissection devices in relation to parathyroid preservation

The Scalpel is an important instrument in surgery used in dissection with the use of conventional methods of hemostasis. Hemostasis is generally achieved with a clamp after dissection at the superior pole. The dissection can cause traction injury to the vessels and damage the parathyroid. It can also shear the vessels leading to a clouded field. Newer devices like harmonic scalpels have minimal lateral thermal injury. They have better control over bleeding including hemostasis of vessels up to 5mm. The field of vision is clear for further dissection. This has reported reduced transient hypocalcaemia from 52 to 45%. Reduction in post-operative drainage in the drainage tubes, avoiding insertion of drainage tubes altogether and transient hypocalcaemia have been the major advantages of the use of harmonic scalpel in most studies (42, 47).

Another device used in recent days is the harmonic focus which functions similar to the harmonic scalpel with more focused energy. This has been compared in several studies with conventional techniques and found to have better results. A meta-analysis published in 2015 reported shorter operative time and hospital stay, lesser blood loss, and reduced hypocalcaemia and nerve injury (48). Despite the usage of these specialized instruments, certain procedures naturally have a higher rate of complications. Total thyroidectomy and central compartment neck dissections are associated with a higher complication rate as compared to hemithyroidectomy (49). The use of magnification loupes as mentioned earlier improves dissection. This has also been reported to reduce transient hypocalcaemia though it comes with a learning curve (39).

Routine vs. selective autotransplantation

Most surgeons prefer a selective approach to autotransplantation, choosing only to autotransplant parathyroid glands which macroscopically appear of dubious viability or were inadvertently removed along with the thyroid specimen. Simply identifying parathyroid glands does not confirm viability as macroscopic assessment is highly subjective and inconclusive. Discoloured glands don't necessarily confer non-viability while a lack of discoloration does not reliably predict an intact blood supply (50, 51). Routine parathyroid autotransplantation was therefore suggested by Delbridge et al. (52) where at least one parathyroid gland was routinely autotransplanted to guard against potential late ischemia in otherwise normal appearing glands. This approach was associated with a higher incidence of temporary hypocalcemia but had the potential to reduce incidence of permanent hypocalcaemia. Selective autotransplantation, however, remains the most widely practiced technique.

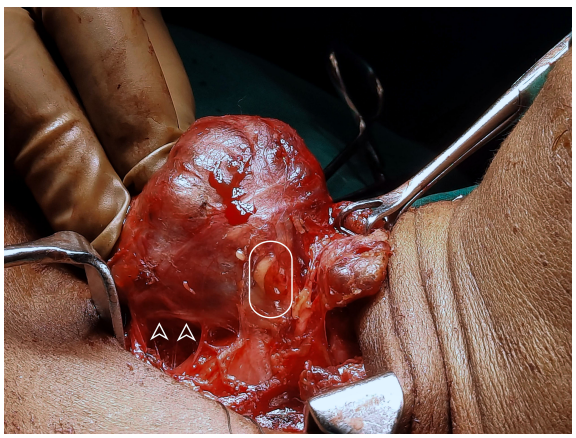

FIGURE 6
Intra-operative picture of thyroid lobe, the intact inferior parathyroid gland (oval) and the recurrent laryngeal nerve (arrowheads).

Nevertheless, the subjective nature and variable ability of surgeons to assess viability of parathyroid glands *in situ* warrants the need for more objective means of assessment (53).

Parathyroid identification and fluorescence and other imaging, PARAFLUO trial

The technique of auto-fluorescence was originally found to be very accurate (29). The detection and preservation of parathyroid using autofluorescence by infrared cameras was nearly 100% accurate as demonstrated by Falco and McWade et al. (54, 55) Autofluorescence is indirect evidence of viable parathyroids while injection of fluorophores followed by detection of fluorescence proves to be more accurate. The injection of indocyanine green dye (ICG) followed by the detection of fluorescence with an infrared camera was studied by Suh and Lavazza et al. in 2015 and 2016 respectively (29, 56, 57). Methylene blue was another contrast agent proposed by Dudley in 1971 (58). Optical coherence tomography, a non-invasive imaging technique for the architectural characterization of parathyroids was proposed by Rubenstein et al. (59, 60) Fluorescence on the other hand was a well-established technique with a few drawbacks like difficulty in differentiation between fat and lymph nodes with a higher false positive rate. They were qualitative methods of detection necessitation quantification of fluorescence. ICG was approved by FDA in 1956 due to its lesser toxicity profile. A very minimal quantity (0.2mg/kg) was sufficient to detect fluorescence with an infrared camera 30 seconds to 2 minutes after injection. This proved to be a real-time, safe, and effective method of parathyroid identification and preservation (56, 57). However, there are contrasting reports too, that post-resection assessment of parathyroids by ICG has been more effective than real-time assessment, thus deeming it not fully competent (40). ICG has a wavelength of about 800nm and can detect parathyroids pre- and post-resection. However, the disadvantage of confusion with other structures which have similar uptake of the dye remains unaddressed. It can also soil the field due to leakage from the vessels (60). It also poses a significate learning curve as opposed to autofluorescence (61, 62). A randomized trial (PARAFLUO) of 245 patients published in 2020 suggested a significant reduction in autotransplantation rates from 13% to 3%, inadvertent parathyroidectomy from 12 to 2.5%, and transient hypocalcaemia from 21.7 to 9.1% (62).

Carbon nanoparticles in LN dissection to preserve parathyroid glands

Carbon nanoparticle (CNP) suspension is a negative technique utilized for the preservation of important structures in thyroid surgery. They have an approximate size of 150 nm. Hence they act as lymphatic tracer that penetrates lymph vessels with a diameter of 120-500nm and not blood vessels that have a diameter of 20-50nm. The thyroid and lymph nodes stain black while the parathyroids and the nerve remain stainless. Parathyroids do not have lymphatic vessels developmentally and the nerves lack lymphatics. This only becomes an indirect technique to identify parathyroids (29). 0.1ml of CNP suspension is injected into superior and inferior thyroid poles away from vital structures. Adjacent blood vessels are kept away from the injection site. After 5 mins, the staining is observed. The rates of lymph node identification and parathyroid preservation were higher with this technique (63). Hagiwara et al. reported the first series using this technique in thyroid surgery (64). The rate of inadvertent parathyroidectomy was reduced by 34% according to a meta-analysis in 2022 (65).

Electrical Impedance spectroscopy (EIS) is another technique that seems promising. It is easy to master and can have wider applications. Adequate software for neck surgeries, suitable techniques to differentiate parathyroid from a lymph node, and also methods of identifying the drop in temperature would be required. Devascularized glands can prove a challenge since these are not visualized in both thyroid and parathyroid surgeries (66).

Laser Speckled Contrast Imaging (LSCI) is an alternative technique to use lasers to detect an interference pattern called the speckled pattern. The movement of blood cells within the vessels causes changes in the speckled pattern based on the flow. This helps us quantify the vascularity in real-time and does not need fluorescence (67). Mannoh et al. published a study suggesting the quantification using LSCI had a sensitivity and specificity of 87% and 84% respectively (68, 69).

Parathyroid auto-transplantation

The first reported parathyroid autotransplant (PTAT) in a human being was performed by William Halsted in 1909. PTAT during thyroid surgery was first reported in 1926, when it was performed during partial thyroidectomy by Lahey (4). The first PTAT after total parathyroidectomy was described in 1968 (70).Viability of the auto-transplanted parathyroid was first reported in 1975 (5, 71). With time, people started acquainting themselves with the techniques of parathyroid autotransplantation and cryopreservation. Gradually, these methods gained popularity as measures to lower rates of hypocalcemia and hypoparathyroidism following total thyroidectomy.

Parathyroid tissue has certain attributes that enable it to survive, thrive and function after autotransplantation.

Imbibition

Immediately after PTAT, the autotransplanted tissue survives by means of imbibition. This refers to the process of passive diffusion of water, oxygen and nutrients into the cells of the graft from the surrounding tissue fluid. The metabolic wastes diffuse out into the surrounding fluid. Grafts can survive by imbibition for up to a week after transplant. The key factors which influence survival of the graft by imbibition are the degree of perfusion of the graft bed

and the size of the bits of tissue that are implanted. There are many reports (72–75) of successful PTAT after transplantation of the tissue within the belly of skeletal muscle, a tissue which is well-perfused and well-oxygenated.

The bits of tissue that are grafted should be small enough to survive the immediate post-operative period, before neo-vascularization. Successful PTAT has been reported with various sizes of the grafts (76–78).

Transplantation of bits of tissue with a volume of $1mm^3$ (1x1x1mm) ensures optimal survival of the tissue. With time, new blood vessels start to develop within the graft by virtue of angiogenesis. Various factors influence this process.

Angiogenesis

The ability of the parathyroid tissue to induce angiogenesis has been shown *in vitro* (79) as well as *in vivo* (80). Vascular endothelial growth factor (VEGF) has been shown to contribute to the development of the angiogenic phenotype *in vitro* (81). Angiogenic activity was observed during the first post-operative week in athymic mice which were subjected to parathyroid auto-transplantation (82). In addition, re-innervation along newly built blood vessels has been demonstrated in transplanted parathyroid tissue 1 week post-operatively (83).

In a trans-species study (76), parathyroid tissue that was harvested from patients was cut into 2x2x1 mm pieces, which were subsequently transplanted into nude mice. Angiogenesis induced by these grafts was detectable by light microscopy on the 5^{th} day after the procedure. Newly grown microvessels were seen to be originating from host venules. Human iPTH was detected in plasma samples of the mice. So, it follows that the donor microvessels served as pathways for sprouting microvessels. Apparently, vascular ingrowths develop in about 10-20 days following implantation (84). Graft function mirrors this process as well and is reflected in serum PTH levels taken during this period.

Site for transplantation

A well-perfused, vascular bed, like skeletal muscle belly, is necessary for autotransplantation in order for the graft to survive by imbibition before new blood vessels are formed by angiogenesis. Generally, the preferred sites for transplantation are the musculature of the forearm and the sternocleidomastoid muscle (72–75).

The advantage of employing the sternocleidomastoid is that another incision can be avoided. Successful PTAT into the brachioradialis has also been reported (78, 79, 85). While it requires a separate incision, it is much easier to assess functioning of the graft. PTAT into pectoralis major has also been reported (75). Funahashi, et al. employed this method in neck dissections. During neck dissection, when the sternocleidomastoid muscle is taped and freed completely, the blood supply to the muscle may be jeopardized, at least transiently. This may adversely affect graft viability. There is a report of successful pre-sternal subcutaneous autotransplantation of parathyroid glands (86).

So, while there are advocates of various sites within the body for implantation of harvested parathyroids, they all concur on the fact that belly of the skeletal muscle is a suitable site for PTAT.

Method of transplantation

The smaller the graft, the more the chances of survival by imbibition. Billings and Milroy (85) have reported successful transplants in which the harvested parathyroid tissue was minced in iced Waymouth's tissue culture medium. The resulting suspension was transplanted into the deltoid and brachioradialis muscles, by means of placement into pockets as well as by injection into the muscles.

In another study (78), the gland which was to be auto-transplanted was sliced into 30 pieces, each of size 1x1x3 mm. These bits were implanted into 30 pockets in the brachioradialis muscle of the forearm.

Testini, et al. (25) employed a technique in which the harvested parathyroid glands were sliced into 1x2mm pieces. One of them was sent for histological confirmation, while the rest of them were immediately autotransplanted into an intramuscular pocket in the sternocleidomastoid on the side of harvest. The site of transplantation was closed with a non-absorbable suture to prevent extrusion of the graft. The grafts were reported to be functional and viable.

Wells SA Jr., et al. (87), in their report about long-term follow-up after PTAT during thyroidectomy, reported that the harvested parathyroid gland was sliced into pieces of size 1x3mm, which were implanted into muscle pockets in the sternocleidomastoid muscle. These were found to be functioning in the long term.

Delbridge, et al. (88) reported successful PTAT after injecting a suspension of finely minced parathyroid tissue into the muscle bulk (Milroy technique). In this study, patients undergoing PTAT were divided into two groups. In the control group (implantation group), PTAT was performed in the conventional method of implanting bits of parathyroid tissue into muscle. In the test group (injection group), PTAT was performed by a novel method of injecting a suspension of finely minced parathyroid tissue into the muscle bulk (Milroy technique). Post-operative assessment included clinical assessment together with estimation of S. Calcium and intact parathormone (iPTH) immediately before the procedure and again on post-op days 1, 14 and 90. In both the groups, the procedure was followed by a fall in mean PTH levels, but it was significant in the implantation group. By 2 weeks, the calcium and iPTH levels had returned to baseline levels. None of the patients developed permanent hypoparathyroidism.

Conclusion

Parathyroid function preservation remains one of the holy grails of thyroid surgery. This helps in limiting not just short term morbidity but also long-term impact on patient health, quality of life and health care costs. Evolution in surgical

technique with capsular dissection, parathyroid identification and autotransplantation in routine use while adjuncts like surgical loupes and energy devices for fine dissection and haemostasis have helped improve outcomes. Questions remain on best practice in terms of selective versus routine parathyroid identification and autotransplantation. Technological advances utilising autofluorescence, laser speckled contrast imaging, electrical impedance spectroscopy and carbon nanoparticle uptake have provided promising potential direct and indirect methods of objective parathyroid identification (89). Nevertheless, parathyroid preservation during thyroid surgery continues to be an art where meticulous surgical technique, experience and expertise remain the mainstays in ensuring good outcomes.

Disclosure

Patients who underwent thyroidectomy were informed about the possibility of usage of operative images for academic purposes and they have given their informed consent for the same.

Author contributions

HR and SSR have jointly written the article. APR, TA and ZM have critically reviewed and edited the article. The latter trio have also provided valuable suggestions and revised the manuscript to its current format. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Application of carbon nanoparticles combined with refined extracapsular anatomy in endoscopic thyroidectomy

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Objective: To evaluate the value of refined extracapsular anatomy combined with carbon nanoparticle suspension tracing technology for protecting parathyroid function and the thoroughness of lymph node dissection in the central region during endoscopic thyroid cancer surgery.

Patients and methods: Retrospective clinical data analysis was performed on 108 patients who underwent endoscopic thyroid cancer surgery at the First Affiliated Hospital of Wannan Medical College (Yijishan Hospital) from November 2019 to November 2022. Before surgery, thyroid function tests, color Doppler ultrasounds and neck-enhanced CT scans were performed on all patients. Cytopathological diagnosis obtained *via* ultrasound-guided fine-needle aspiration served as confirmation for the primary diagnosis. It was determined whether to perform a total thyroidectomy or a hemithyroidectomy (HT) together with preventive unilateral (ipsilateral) central neck dissection. Follow-up times were 1 to 34 months.

Results: Transient neuromuscular symptoms were present in 3.70% (4/108) cases, with no permanent neuromuscular symptoms or permanent hypoparathyroidism. Regarding transient hypoparathyroidism, the patients recovered after three months and did not need long-term calcium supplementation. The number of harvested LNs (mean± SD) was 5.54 ± 3.84, with ≤5 in 57.41% (62/108) and >5 in 42.59% (46/108) cases. The number of patients with metastatic LNs was 37.96% (41/108), with ≤2 in 65.85% (27/41) and >2 in 34.15% (14/41) cases.

Conclusions: Fine extracapsular anatomy combined with carbon nanoparticle suspension tracing is effective in endoscopic thyroid cancer surgery. It can improve the thoroughness of prophylactic central neck dissection and recognition of the parathyroid gland and avoid parathyroid injury and other complications to effectively protect parathyroid function.

KEYWORDS

extracapsular anatomy, carbon nanoparticles, endoscopic thyroid cancer surgery, hypoparathyroidism, prophylactic central neck dissection

Introduction

According to the global IARC tumor registration report on five continents, the incidence of thyroid cancer increased sharply from 1973 to 2002, and the incidence rate in women was three times higher than in men (1). According to statistics from the China Cancer Center, the age-standardized incidence rate of thyroid cancer in China was 168.08/100000 in 2012, with the age-standardized incidence rate in women being 169.4/100000 (2). The incidence rate of thyroid cancer in China is increasing at an annual rate of 5.92%, which is 4% higher than the global incidence rate. Moreover, the incidence in big cities is higher than that in rural areas. Overall, the incidence rate in females is higher than that in males (3–5). Due to the development of urbanization and improvement of economic conditions, women have higher esthetic requirements. To avoid neck scars, endoscopic thyroid surgery is increasingly carried out to improve the cosmetic effect (6, 7). Protecting the parathyroid gland versus the thoroughness of lymph node dissection in the central region during endoscopic thyroid cancer surgery has remained controversial. When the parathyroid gland is injured, parathyroid hormone levels may decrease, which may cause the patient to experience various symptoms, including perioral numbness and convulsions. Incomplete dissection of lymph nodes in the central region is an important reason for local recurrence after the operation. Indeed, a recent retrospective analysis of 399 patients showed that thorough lymph node dissection in the central region can significantly increase the disease-free survival (DFS) after thyroid cancer surgery, especially with respect to occult lymph node metastasis, which is an important factor affecting prognosis (8). Moreover, intraoperative use of indocyanine green and carbon nanoparticle suspensions as tracers can protect the parathyroid gland and increase the thoroughness of lymph node dissection in the central region (9). Our department uses a carbon nanoparticle suspension to trace lymph nodes during surgery in an effort to improve the thoroughness of lymph node dissection in the central area, protect parathyroid function, and reduce postoperative complications and local recurrence. As a new type of lymphatic tracer, carbon nanoparticles (CNs) have an active movement mechanism. CNs are phagocytosed by macrophages and then enter the lymphatic capillaries and accumulate in lymph nodes, such that the thyroid gland and lymph nodes in the drainage area quickly become blackened according to the order of thyroid lymphatic drainage (10, 11). As there are no communicating lymphatic vessels between the thyroid tissue and the parathyroid gland, the thyroid tissue and surrounding lymph nodes become stained black after CNs are injected into the thyroid tissue, whereas the parathyroid gland remains unstained. This is called the "negative parathyroid imaging effect" and is used to protect the parathyroid gland (12). In this study, we sought to assess the application value of refined extracapsular anatomy combined with a CNs suspension for protecting parathyroid function and lymph node dissection in the central region during endoscopic surgery for thyroid cancer.

Abbreviations: HT, hemithyroidectomy; IARC, international agency for research on cancer; CNs, carbon nanoparticles; CND, central neck dissection; TNM, tumor, regional lymph node, metastasis.

Materials and methods

Patient enrollment

Clinical data for 108 patients with thyroid cancer who underwent surgery at the First Affiliated Hospital of Wannan Medical College from November 2019 to November 2022 were analyzed retrospectively. All patients underwent thyroid function measurement, color Doppler ultrasound examination and neck enhanced CT examination before the surgery. Diagnoses were confirmed by cytopathology based on fine-needle aspiration under ultrasound guidance.

Criteria for inclusion

(1) No history of neck surgery; (2) normal parathyroid gland function; (3) papillary thyroid carcinoma; (4) no invasion of the thyroid envelope; (5) enhanced CT showing no lateral cervical lymph node metastasis; and (6) no abnormalities in preoperative routine blood tests, blood coagulation function tests, chest CT, fiberoptic laryngoscopy, liver and kidney function tests or electrolyte examination.

Criteria for exclusion

(1) History of neck radiotherapy; (2) hyperthyroidism; (3) Hyperparathyroidism; (4) medullary thyroid carcinoma or anaplastic thyroid cancer; (5) thyroid tumor recurrence.

Surgical procedure and CN suspension injection

All operations were performed by a professional and experienced thyroid surgeon. Endoscopic radical thyroidectomy was performed *via* the oral vestibule, the axillo-breast approach, and the areolar approach. The thyroid gland was exposed, and the integrity of the thyroid surgical capsule was maintained according to the principle of membrane anatomy (Figure 1A). CNs (0.1-0.2 ml) were drawn into a 1-mL skin test syringe, and the thyroid gland was punctured at a depth of 5 mm (Figure 1B). The CNs were slowly injected into the tissue around the gland tumor on the affected side under the true capsule (Figure 1C). During the injection, it is necessary to avoid the tumor and blood vessels and to slowly inject after drawing back blood to prevent the CN suspension from entering the blood vessels; the injection volume was 0.1-0.2 mL. After the injection, a gauze strip was pressed for a moment to prevent CN overflow, as overflowing CNs easily blacken the surgical field, affecting the operation. The CNs diffuse into the thyroid tissue within 3 min. We also found some lymph nodes stained black at the

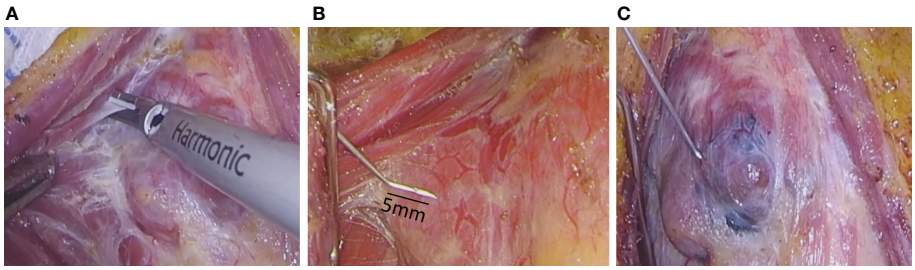

FIGURE 1
Refined extracapsular anatomy and injection of carbon nanoparticles suspension. **(A)** refined extracapsular anatomy **(B)** The needle tip of the syringe is bent by 5mm **(C)** slow injection of carbon nanoparticles suspension.

central compartment of the neck, though the parathyroid glands were not stained. Endoscopic thyroidectomy and prophylactic lymph node dissection were performed in the central region (13). Due to the negative development of CNs, we carefully looked for the inferior parathyroid gland and kept it in place to avoid damaging the parathyroid vessels (Figure 2A). The anterior branch of the superior thyroid artery was slowly coagulated with an ultrasonic knife, and we operated close to the gland to avoid damaging the external branch of the superior laryngeal nerve. The posterior branch of the superior thyroid artery was maintained as much as possible; that is, the "off hat method" was used for the superior thyroid. The superior parathyroid gland can generally be clearly identified and retained *in situ* (Figure 2B) (14, 15). Lymph node dissection in the central area was performed after thyroid cancer was confirmed by the frozen section procedure during the operation. As CNs track the lymph nodes, they become stained black, which is conducive to dissection of lymph nodes in the central area (Figures 3A, B).

Observations

(1) The time needed for the operation, total amount of postoperative drainage, drainage time and postoperative hospital stay were noted.(2) The number of cases with transient hoarseness and permanent hoarseness was assessed. (3) The number of cases with transient hypocalcemia neuromuscular symptoms and permanent neuromuscular symptoms and the incidence of transient and permanent hypoparathyroidism were also evaluated. (4) The number of lymph nodes removed and the number of positive lymph nodes in the central area were recorded.

Statistical analysis

SPSS 22.0 software (Chicago, IL, USA) was used for statistical analyses. Continuous variables are expressed as mean ± standard deviations (SDs). A P value less than 0.05 was considered statistically significant.

Results

Characteristics of patients

A total of 108 patients underwent successful endoscopic thyroidectomy. The demographics are shown in Table 1. There were 4 males and 104 females, ages ranged from 15 to 54 years, with an average age of 30.98 ± 6.38 years. Height (cm) (mean ± SD) of the patients was 162.16 ± 4.43, weight (kg) (mean ± SD) was 58.54 ± 8.70, and body mass index (BMI) (mean ± SD) was 22.39 ± 3.50.

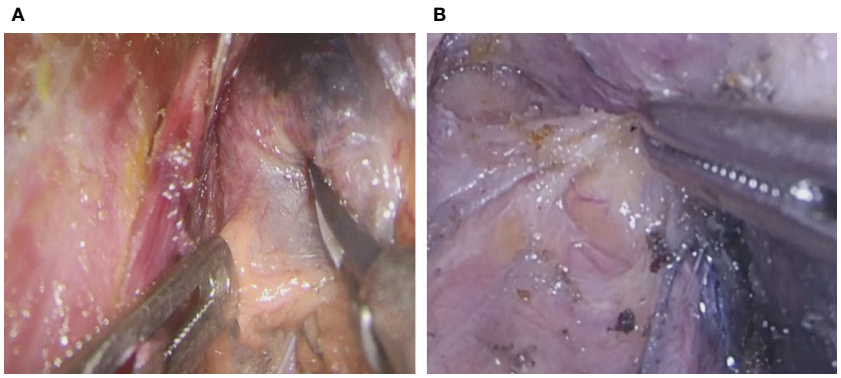

FIGURE 2
Parathyroid gland expose. **(A)** Inferior parathyroid gland **(B)** Superior parathyroid gland.

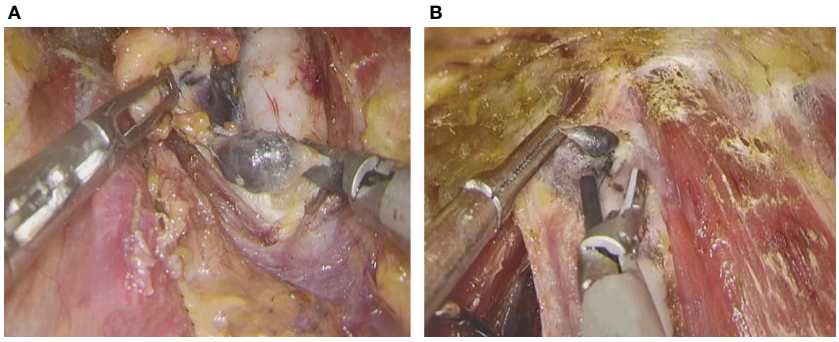

FIGURE 3
Resection of lymph nodes. **(A)** resection of lymph nodes on pre-tracheal **(B)** resection of anterior laryngeal lymph nodes.

TABLE 1 Clinical data of patients.

Characteristics of patients (n = 108)	Absolute NO.	Relative %
Age, years (mean ± SD)	30.98±6.38	
Age(years)		
≤55	108	100%
>55	0	0%
Gender		
Male	4	3.70%
Female	104	96.30%
Height (cm) (mean ± SD)	162.16±4.43	
Height (cm)		
≤160	47/108	43.52%
>160	61/108	56.48%
Weight (kg) (mean ± SD)	58.54±8.70	
Weight (kg)		
≤60	75	69.44%
>60	33	30.56%
BMI (mean ± SD)	22.39±3.50	
≤25	92	85.19%
>25	16	14.81%
Tumor site		
Middle /Upper portion	31/108	28.70%
Middle	31/108	28.70%
Middle / lower portion	46/108	42.60%
Tumor Side		
left	48/108	44.44%
right	60/108	55.56%

SD, standard deviation; BMI, body mass index.

Tumor sites were as follows: middle/upper portion 31, middle 31, middle/lower portion 46.

Carbon nanoparticles improves the protective effect on the parathyroid gland

Data for the patient operations are shown in Table 2. The operation paths were as follows: 32 cases of the oral vestibule, 56 cases of the axillo-breast approach and 20 cases of the areolar approach. Six patients underwent total thyroidectomy + central neck dissection (CND) and 102 hemithyroidectomy +CND. Postoperative transient hoarseness occurred in 3/108 (2.77%) patients, with no cases of permanent hoarseness. Only 3 patients experienced hoarseness and recovered after one month of medical therapy. Transient neuromuscular symptoms occurred in 4/108 (3.70%) patients; there were no permanent neuromuscular symptoms. No permanent hypoparathyroidism occurred. Those who experienced transient hypoparathyroidism recovered after three months, with no need for long-term calcium supplementation. CNs can significantly prevent parathyroid injuries. There was no recurrence in our cohort. The operation time was 156.94 ± 44.48 minutes, and the total postoperative drainage was 149.69 ± 53.05 ml. The postoperative drainage time was 3.46 ± 0.65 day. The postoperative hospital stay time was 3.49 ± 0.65 day.

Carbon nanoparticles facilitate harvesting of lymph nodes

The postoperative pathological characteristics were shown in Table 3. Mean tumor size was 0.72 ± 0.28 cm, 88.89%(96/108) patients with a tumor ≤1 cm and 11.11%(12/108) with a tumor >1 cm. The average numbers of harvested LNs were 5.54 ± 3.84. There were 57.41% (62/108) patients have ≤5 LNs and 42.59% (46/108) have >5 LNs. There were 37.96% (41/108) patients have metastatic LNs. The average numbers of metastatic LNs were 0.91 ± 1.74. There were 65.85% (27/41) patients have ≤2 metastatic LNs and 34.15% (14/41) have >2 metastatic LNs. For all the 108 patients, Histological grading was grade I, and pathological TNM staging was stage I.

TABLE 2 Operation and post operation condition.

Characteristics of patients (n = 108)	Absolute NO.	Relative %
Operation path		
Transoral vestibule	32	29.62%
Transthoracic breast	56	51.85%
Transaxillary	20	18.53%
Extent of surgery		
total thyroidectomy +CND	6/108	5.56%
hemi thyroidectomy +CND	102/108	94.45%
Postoperative hoarseness		
Transient	3/108	2.77%
Permanent	0	0%
Neuromuscular symptoms		
Transient	4/108	3.70%
Permanent	0	0%
Hypoparathyroidism		
Transient	5/108	4.62%
Permanent	0	0%
Recurrence	0	0%
Operation time (mins, mean± SD)	156.94±44.48	
Total postoperative drainage (ml, mean±SD)	149.69±53.05	
Postoperative drainage time (day, mean ±SD)	3.46±0.65	
Postoperative hospital stay time (day, mean ±SD)	3.49±0.65	

CND, central neck dissection; SD, standard deviation.

TABLE 3 Characteristics postoperative pathological.

Characteristics of patients (n = 108)	Absolute NO.	Relative %
Tumor size(cm)(mean ± SD)	0.72±0.28	
≤1	96/108	88.89%
>1	12/108	11.11%
Pathological type		
Papillary carcinoma	108/108	100%
Other types	0	0%
Numbers of harvested LNs (Pieces mean± SD)	5.54±3.84	
≤5	62/108	57.41%
>5	46/108	42.59%
metastatic LNs (Pieces mean± SD)	0.91±1.74	
≤2	27/41	65.85%
>2	14/41	34.15%
Numbers of patients with metastatic LN		
LN positive	41/108	37.97%
LN negative	67/108	62.03%
Histological grading		
I	108/108	100%
II-III	0	0%
Pathological staging		
I	108/108	100%
II	0	0%
III	0	0%

LNs, lymph nodes; SD, standard deviation.

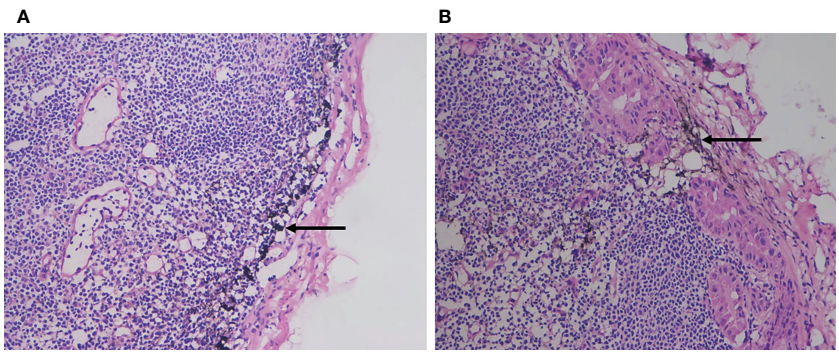

FIGURE 4
The tracing effect of CNs. **(A)** The carbon nanoparticles were located in the marginal sinus of the lymph node without metastasis of the tumor **(B)** The carbon nanoparticles were located in the marginal sinus of the lymph node where the tumor had metastasis.

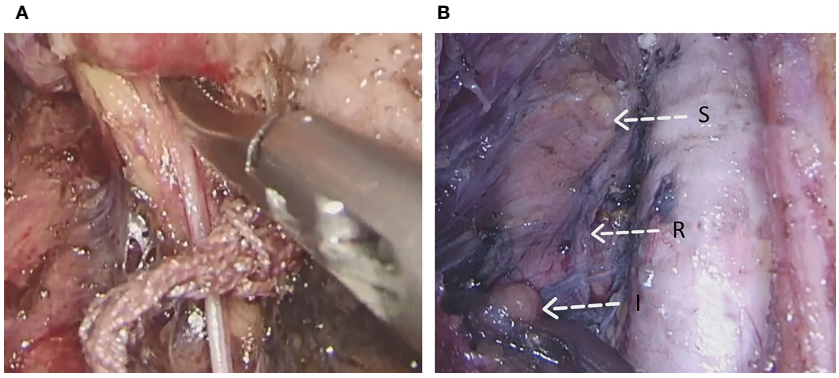

FIGURE 5
Laryngeal nerve and parathyroid gland protecting. **(A)** establishment of recurrent laryngeal nerve tunnel to protecting **(B)** Surgical field after thyroidectomy (S, Superior parathyroid gland; R, Recurrent laryngeal nerve; I, Inferior parathyroid gland).

Discussion

Currently, the majority of young patients have accepted endoscopic thyroid surgery because of its advantages, such as minimal invasiveness and scarless. This approach has the advantages of enlarging the surgical area and high resolution of the surgical field of view. There were only 4 males but 104 females in our study, and average age was 30.98 ± 6.38 years old. May be young women have high requirements for beauty, and there is an advantage of scarlessness in endoscopic radical thyroidectomy.

Whether it can effectively protect the parathyroid gland and completely remove the lymph nodes in the central region has been the focus of controversy. In general, endoscopic lymph node dissection is difficult without navigation for tracking the lymph nodes. Therefore, searching for effective materials for lymph node navigation and tracking is a hot research topic. As a new lymphatic tracer, CNs have the advantages of rapid staining, long duration and clear lymphatic tracing, and they have been applied in both open thyroid cancer surgery and endoscopic thyroid cancer surgery. CNs have an active movement mechanism, whereby they are engulfed by macrophages and then enter the lymphatic capillaries, accumulating in the lymph nodes. Thus, the thyroid gland and lymph nodes in the drainage area quickly become blackened according to the order of thyroid lymphatic drainage (10, 11). CNs can help surgeons to distinguish between lymph nodes and fat particles. Some studies have shown that the small lymph nodes (diameter<5 mm) in the central area and the relatively hidden lymph nodes are difficult to identify during the cleaning process and are easily ignored. With CN staining and the magnifying effect of endoscopy, the operator can easily find and remove the small lymph nodes in this area, significantly promoting the thoroughness of lymph node cleaning (16, 17). The number of harvested LNs was 5.54 ± 3.84 in our study. Compared with a retrospective cohort study, 114 PTC patients undergoing bilateral axillo-breast approach robotic thyroidectomy (BABART) were enrolled and divided into CNs group (n=64) and control group (n=50). The mean number of retrieved central lymph node was significantly higher in the CNs group than in the control group (9.48 ± 4.88 vs. 5.40 ± 2.67, P<0.001) (18). The other prospective randomized study, three hundred two consecutive early-stage thyroid cancer patients eligible for endoscopic thyroidectomy *via* bilateral areola approach (ETBAA) were recruited and divided into two group: a carbon nanoparticles group (n=152) and a control group (n=150). The total number of dissected lymph nodes was 1059 in the carbon nanoparticles group and 872 in the control group (P=0.00) (19). The applying of carbon nanoparticle can help to detect lymph nodes and increase the number of lymph nodes visualized and preserved.

In addition, the tracing effect of CNs has a guiding role for pathologists to take lymph nodes after surgery, reducing the impact of human factors on the number of lymph nodes (Figures 4A, B) (20). In preventive lymph node dissection in the central region, CNs can be used as a tracer to make the parathyroid gland easy to identify, avoiding the risk of injury to the recurrent laryngeal nerve and parathyroid gland (Figures 5A, B) (21). In fact, parathyroid gland injury can lead to a decrease in parathyroid hormone, and patients will have symptoms such as perioral numbness and hypocalcemia convulsions. If permanent hypoparathyroidism occurs, long-term oral or intravenous calcium supplementation is needed, which affects quality of life (22, 23). When CNs are injected into the thyroid tissue, the surrounding lymph nodes stain black, though the parathyroid gland does not. When the thyroid gland is removed, fine envelope dissection is used to protect the nonblack-stained tissue as much as possible, reducing the risk of parathyroid damage during lymph node dissection of thyroid cancer (24). As there are no lymphatic vessels communicating between the thyroid tissue and the parathyroid gland, the thyroid tissue and surrounding lymph nodes are stained black after CNs are injected into the thyroid tissue, whereas the parathyroid gland remains unstained. This “negative parathyroid imaging effect” achieves localization, recognition and protection of the parathyroid gland and reduces the incidence of postoperative hypothyroidism (12). However, it has been reported that through the whole areola approach in

endoscopic thyroid cancer surgery, the use of CNs cannot significantly enhance protection of the parathyroid glands, especially the lower parathyroid gland, and cannot significantly benefit protection of the parathyroid glands or lymph node dissection (25, 26). In our study, 2.77% (3/108) patients suffered transient postoperative hoarseness and 4.62% (5/108) patients appeared transient hypoparathyroidism. According to a meta-analysis, the median incidence of transient and permanent hypoparathyroidism was 27% (19%-38%) and 1% (0-3%) respectively (27). Another study based on the SEER-Medicare linked database shows that 11% of the cases need calcium and vitamin D supplementation for hypoparathyroidism (28). Furthermore, the immune response caused by residual CNs in the thyroid bed may increase tissue inflammation and edema, thus reducing the venous flow of the parathyroid gland, which has a negative impact on parathyroid gland function (29).

There are also some limitations of our study. Firstly, all the 108 patients received endoscopic thyroid cancer surgery and the CNs was used during operation. And we don't get the data of patients without using CNs. However, there are many similar research in the literature, and our data ware basically consistent with others. Secondly, many postoperative symptoms were collected, but little objective indicator, like serum PTH and Ca^{2+} level, was tested. Mainly because that we didn't test PTH or Ca^{2+} level after surgery routinely in our center, unless bilateral thyroidectomy was performed or patients with overt symptom. And we are preparing to conduct a prospective study in the near future.

Conclusion

In summary, the application of refined extracapsular anatomy combined with a CN suspension tracing technology has a definite effect in endoscopic thyroid cancer surgery, improving the thoroughness of preventing lymph node dissection in the central region, enhancing recognition of the parathyroid gland, and avoiding parathyroid injury or accidental resection as well as other complications, thus effectively preserving parathyroid function.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the (Yijishan Hospital) First Affiliated Hospital of Wannan Medical College. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. The study protocol was approved by the Ethics Committee of the (Yijishan Hospital) First Affiliated Hospital of Wannan Medical College. Informed consent was obtained from all individual participants included in the study.

Author contributions

The article was mainly written by ZW and RS. ZW, HB, YX, and ZB, these authors contributed equally to the study, ZW, HB, YX, EL, XS and ZB helped with data analysis and paper editing. YW, ZW, ZY, and CY did an operation study. The whole study was instructed by BC, YW and RS. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Maximal parathyroid gland diameter as a predictive factor for autograft-dependent recurrent secondary hyperparathyroidism after total parathyroidectomy

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Introduction: Following total parathyroidectomy (PTx), transcervical thymectomy, and forearm autograft for secondary hyperparathyroidism (SHPT), recurrent SHPT can occur in the autografted forearm. However, few studies have investigated the factors contributing to re-PTx due to autograft-dependent recurrent SHPT before the completion of the initial PTx.

Methods: A total of 770 patients who had autografted parathyroid fragments derived from only one of the resected parathyroid glands (PTGs) and who had undergone successful initial total PTx and transcervical thymectomy—defined by serum intact parathyroid hormone level < 60 pg/mL on postoperative day 1—between January 2001 and December 2022 were included in this retrospective cohort study. Factors contributing to re-PTx due to graft-dependent recurrent SHPT before the completion of the initial PTx were investigated using multivariate Cox regression analysis. Receiver operating characteristic (ROC) curve analysis was performed to obtain the optimal maximum diameter of PTG for autograft.

Results: Univariate analysis showed that dialysis vintage and maximum diameter and weight of the PTG for autograft were significant factors contributing to graft-dependent recurrent SHPT. However, multivariate analysis revealed that dialysis vintage (P=0.010; hazard ratio [HR], 0.995; 95% confidence interval [CI], 0.992–0.999) and the maximum diameter of the PTG for autograft (P=0.046; HR, 1.107; 95% CI, 1.002–1.224) significantly contributed to graft-dependent recurrent SHPT. ROC curve analysis showed that < 14 mm was the optimal maximum diameter of PTG for autograft (area under the curve, 0.628; 95% CI, 0.551–0.705).

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Conclusions: The dialysis vintage and maximum diameter of PTG for autograft may contribute to re-PTx due to autograft-dependent recurrent SHPT, which can be prevented by using PTGs with a maximum diameter of < 14 mm for autograft.

KEYWORDS

secondary hyperparathyroidism, parathyroidectomy, recurrent secondary hyperpara thyroidism, autograft, parathyroid gland

1 Introduction

Patients with prolonged chronic kidney disease often experience secondary hyperparathyroidism (SHPT) (1). Calcimimetics can be a treatment of choice for managing SHPT (2). However, some patients are refractory to medical treatment or cannot take calcimimetics. Consequently, parathyroidectomy (PTx) is the final treatment option for these patients. There are various surgical procedures for treating SHPT, including subtotal PTx that involves removing 3.5 parathyroid glands (PTGs) while leaving 40–80 mg of PTG tissue in the neck to prevent hypoparathyroidism. Autografting is not necessary during subtotal PTx, and previous reports have shown that similar clinical outcomes can be obtained with subtotal PTx as with total PTx and autograft (3, 4). However, there is a potential risk of dissemination and recurrent SHPT due to the remaining PTG, which is a concern (5). Subtotal PTx is recommended for patients who anticipate kidney transplantation in the near future (6, 7). As improved kidney function does not stimulate the remaining PTG, it can prevent recurrent SHPT. However, for patients who require long-term dialysis or anticipate kidney transplantation, total PTx, transcervical thymectomy, and forearm autograft are recommended (6). These surgical procedures can prevent persistent or recurrent SHPT in the neck area, and any recurrent cases of SHPT owing to autografted PTGs in the forearm can be easily removed under local anesthesia (6). Total PTx, transcervical thymectomy, and forearm autograft are commonly performed (8). Previous reports have demonstrated the efficacy of PTx in improving several clinical outcomes, such as bone density, osteodystrophy, cardiovascular events, and mortality (1, 9–12). However, persistent or recurrent SHPT, which can occur in the neck or mediastinal area and in the autografted forearm after the initial PTx, remains a serious problem, resulting in re-PTx (13, 14). Previous studies have often investigated persistent or recurrent SHPT in the neck or mediastinal area following initial PTx (14, 15). Remnant PTGs in the neck or mediastinal area after initial PTx are stimulated under chronic kidney disease conditions, leading to the causative PTGs for persistent or recurrent SHPT (14, 15). PTGs causing persistent or recurrent SHPT are usually refractory to medical treatment and require re-PTx (15). However, re-PTx in the neck or mediastinum area can lead to surgical complications, including recurrent laryngeal nerve injury and postoperative bleeding because of the adhesion due to the initial PTx (16). Several methods have been investigated to prevent re-PTx in the neck or mediastinum area, including the efficacy of preoperative imaging studies, intraoperative parathyroid hormone (PTH) monitoring, and frozen section diagnosis (17–21). However, it is important to note that graft-dependent recurrent SHPT can still occur as autografted parathyroid fragments can be stimulated under chronic kidney disease conditions. Although the incidence of graft-dependent recurrent SHPT is low (only 5%) and causative PTGs in the forearm can easily be removed under local anesthesia (22), preventive measures should still be taken, because re-PTx for graft-dependent recurrent SHPT can be burdensome for patients. Therefore, equal attention should be given to investigating preventative measures for graft-dependent recurrent SHPT and persistent or recurrent SHPT in the neck or mediastinal area. However, few studies have investigated the factors contributing to graft-dependent recurrent SHPT (22, 23). Previously identified contributing factors were based solely on pathological findings (23). However, the results of pathological findings are obtained after the operation and cannot be used to select optimal PTGs for autograft during operation. A thorough understanding of contributing factors to prevent graft-dependent recurrent SHPT, especially those that occur before initial PTx completion, may enable the selection of optimal PTGs from the resected PTGs and help prevent graft-dependent recurrent SHPT. This study aimed to investigate the factors contributing to graft-dependent recurrent SHPT before the completion of initial PTx.

Abbreviations: CI, confidence interval; HR, hazard ratio; PTG, parathyroid gland; PTH, parathyroid hormone; PTx, parathyroidectomy; SHPT, secondary hyperparathyroidism.

2 Materials and methods

2.1 Study design

This retrospective cohort study was approved by the Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital Institutional Review Board (approval number: 1577; Aichi, Japan). Factors contributing to graft-dependent recurrent SHPT before initial PTx completion were investigated. The study was conducted in accordance with the principles of the Declaration of Helsinki and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

2.2 Participants

Patients who underwent successful initial total PTx and transcervical thymectomy and received autografted parathyroid fragments derived from only one of the resected PTGs at our center between January 2001 and December 2022 were included in this retrospective cohort study (n = 770). To minimize the impact of persistent or recurrent SHPT due to PTGs in the neck or mediastinum, only those patients who had a successful initial PTx were selected. Patients were followed up at 1, 3, 6, and 12 months and annually after PTx. All patient data were collected retrospectively from medical records and analyzed anonymously; therefore, obtaining informed consent from the participants was not required.

2.3 Indications of initial PTx and Re-PTx for SHPT

According to the Japan's Chronic Kidney Disease-related Mineral and Bone Disorder guidelines (24), the following patients were indicated for initial PTx or re-PTx in cases of SHPT: those with intact PTH levels of ≥ 500 pg/mL; those with uncontrolled levels of serum calcium (> 10.0 mg/dL) or phosphorus (> 6.0 mg/dL) even after medical treatment; or those with SHPT symptoms.

2.4 Surgical procedure of initial PTx

All patients underwent total parathyroidectomy, transcervical thymectomy, and forearm autograft. The PTGs that appeared most similar to the normal PTGs were selected for autografts. The PTGs were fragmented into 1 × 1 × 3 mm pieces. Thirty fragmented pieces were autografted into the forearm muscle (25).

2.5 Definition of successful initial PTx and hypoparathyroidism

As per the Chronic Kidney Disease-related Mineral and Bone Disorder guidelines in Japan, the target range for the serum intact PTH level is 60–240 pg/mL (19). Therefore, serum intact PTH level of < 60 pg/mL on postoperative day 1 was defined as a successful initial PTx. The validity of this definition has been confirmed in previous reports (17, 18). The incidence of re-PTx due to persistent or recurrent SHPT in the neck or mediastinum was significantly lower in patients with serum intact PTH levels < 60 pg/mL on postoperative day 1 than in those with PTH levels ≥ 60 pg/mL. Hypoparathyroidism was defined as persistent serum intact PTH levels < 60 pg/mL after initial PTx.

2.6 Pathological findings of PTGs

Pathologists investigated paraffin sections of resected PTGs, and the following hyperplastic patterns were identified: diffuse hyperplasia, concomitant diffuse and nodular hyperplasia, and nodular hyperplasia (26).

2.7 Diagnosis of localization of causative PTGs for Re-PTx

The localization of causative PTGs for re-PTx was diagnosed using computed tomography, ultrasonography, and technetium-99m methoxyisobutylisonitrile scintigraphy for persistent or recurrent SHPT in the neck or mediastinum and using ultrasonography and magnetic resonance imaging for recurrent SHPT in the autografted forearm (19, 25).

2.8 Surgical approach for Re-PTx in graft-dependent recurrent SHPT

Re-PTx was performed under local anesthesia, and the autografted PTGs in the forearm muscle were removed with the surrounding muscle to prevent the recurrence of the remaining small PTG fragments (25).

2.9 Statistical analysis

Categorical variables were analyzed using the chi-squared test or Fisher's exact test, whereas continuous variables were analyzed using the Mann–Whitney U test. Cox regression analysis was performed to investigate the factors contributing to re-PTx due to graft-dependent recurrent SHPT and to the prevention of hypoparathyroidism after initial PTx. The analysis included all the following covariates: sex, age, height, body weight, body mass index, diabetic nephropathy, dialysis vintage, preoperative vitamin D receptor activation therapy, preoperative calcimimetic therapy, preoperative serum alkaline phosphatase level, preoperative serum calcium level corrected by serum albumin level, preoperative phosphorus level, serum intact PTH level at admission, maximum diameter and weight of PTG for autograft, and the number of fragmented parathyroid pieces for autograft.

To investigate the impact of the hyperplastic pattern of the PTGs on graft-dependent recurrent SHPT, Cox regression analysis adjusted for dialysis vintage, the maximum diameter of PTG for autograft, and the weight of PTG for autograft was performed. To investigate the impact of the hyperplastic pattern of PTGs on contributing factors to prevent hypoparathyroidism after PTx, Cox regression analysis adjusted for dialysis vintage, maximum diameter and weight of PTG for autograft, and preoperative vitamin D receptor activation therapy was performed. Receiver operating characteristic (ROC) curve analysis was performed to obtain the optimal maximum diameter of PTG for autograft. Statistical analyses were performed using IBM SPSS® Statistics for Windows (version 23.0; IBM Corp., Armonk, NY, USA) and R version 4.0.2 (R Core Team (2020)). Statistical significance was set at P value < 0.05 for all analyses.

3 Results

3.1 Study population

Between January 2001 and December 2022, a total of 1,755 procedures involving PTx, transcervical thymectomy, and forearm autograft were performed. Of these, successful PTx was performed in 1,622 patients (92.4%), while it was unsuccessful in 133 patients (7.6%). Among the 1,622 patients with successful PTx, 770 had parathyroid fragments autografted from only one PTG, while the remaining 852 had parathyroid fragments autografted from ≥ 2 PTGs. The median observation period for the patients included in the final analysis (n = 770) was 47.0 months (interquartile range, 17.0–89.0). The patients were classified into two groups based on re-PTx or non-re-PTx for graft-dependent recurrent SHPT (Figure 1).

3.2 Patient characteristics

With respect to patient characteristics, no significant differences were identified between the two groups, except for dialysis vintage (P = 0.003), preoperative serum calcium level (P = 0.008), preoperative serum calcium level corrected by serum albumin level (P = 0.003), preoperative serum phosphorus level (P = 0.009), and serum intact PTH level at admission (P = 0.027) (Table 1).

3.3 Intraoperative and postoperative findings

Significant differences were identified between the two groups with respect to the maximum diameter (P = 0.001) and weight (P < 0.001) of the PTG for autograft (Table 2). Significant differences were identified between the two groups in terms of several variables. These included serum phosphorus levels on postoperative day 1 (P = 0.028), serum intact PTH levels on postoperative day 1 (P = 0.012), incidence of hypoparathyroidism after initial PTx (P < 0.001), and observation period (P = 0.003) (Table 2). Although postoperative management, including calcium supplementation therapy, vitamin D receptor activation therapy, and kidney transplantation after PTx, was similar in both groups, a higher frequency of postoperative calcimimetics therapy was observed in the re-PTx group (P < 0.001).

3.4 Factors contributing to Re-PTx due to graft-dependent recurrent SHPT before the completion of the operation

Univariate Cox regression analysis of the factors contributing to re-PTx for graft-dependent SHPT before the completion of operation demonstrated significant differences in dialysis vintage (P = 0.007; hazard ratio [HR], 0.995; 95% confidence interval [CI], 0.991–0.999), maximum diameter of PTG for autograft (P = 0.002; HR, 1.119; 95% CI, 1.041–1.202), and weight of PTG for autograft (P = 0.024; HR, 1.001; 95% CI, 1.000–1.002) (Table 3). Multivariate Cox regression analysis demonstrated significant differences in dialysis vintage (P = 0.010; HR, 0.995; 95% CI, 0.992–0.999) and the maximum diameter of PTG for autograft (P = 0.046; HR, 1.107; 95% CI, 1.002–1.224) (Table 4).

3.5 Impact of hyperplastic pattern on Re-PTx due to graft-dependent recurrent SHPT

No significant differences were identified regarding the impact of the hyperplastic pattern of autografted PTGs on re-PTx for graft-dependent recurrent SHPT both in unadjusted (P = 0.568) and adjusted Cox regression analyses for dialysis vintage and in maximum diameter and weight of PTG (P = 0.732) (Table 5).

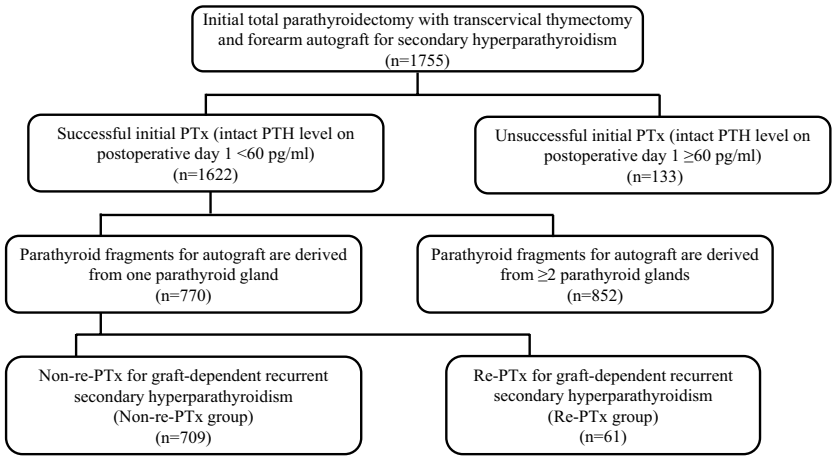

FIGURE 1
Patient flow chart.

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TABLE 1 Patient characteristics.

	Non-re-PTx group $n = 709$	Re-PTx group $n = 61$	P value	OR	95% CI	
Sex (male), n (%)	403 (56.8)	34 (55.7)	0.867	0.956	0.565	1.619
Age (years), mean (SD)	55.3 (11.4)	54.0 (12.3)	0.450			
Height (cm), mean (SD)	160.8 (9.5)	161.8 (10.4)	0.495			
Body weight (kg), mean (SD)	58.0 (13.1)	57.7 (11.2)	0.727			
Body mass index (kg/m^2), mean (SD)	22.3 (3.7)	22.0 (3.2)	0.756			
Dialysis vintage (months), mean (SD)	145.5 (96.8)	111.2 (48.6)	**0.003**			
Diabetic nephropathy, n (%)	78 (11.0)	3 (4.9)	0.190	0.418	0.128	1.367
Preoperative vitamin D receptor activation therapy, n (%)	533 (75.2)	42 (68.9)	0.116	0.635	0.359	1.123
Preoperative calcimimetic therapy, n (%)	216 (30.5)	14 (23.0)	0.245	0.678	0.366	1.259
Preoperative serum albumin level (g/dL), mean (SD)	3.6 (0.5)	3.5 (0.5)	0.082			
Preoperative serum alkaline phosphatase level (U/L), mean (SD)	451.3 (428.4)	447.0 (357.8)	0.874			
Preoperative serum calcium level (mg/dL), mean (SD)	10.0 (0.8)	10.2 (0.6)	**0.008**			
Preoperative serum calcium level corrected by serum albumin level (mg/dL), mean (SD)	10.4 (0.9)	10.8 (0.8)	**0.003**			
Preoperative serum phosphorus level (mg/dL), mean (SD)	6.2 (4.5)	6.6 (1.6)	**0.009**			
Serum intact PTH level at admission (pg/mL), mean (SD)	882.3 (559.9)	998.9 (515.2)	**0.027**			

CI, confidence interval; OR, odds ratio; PTH, parathyroid hormone; PTx, parathyroidectomy; SD, standard deviation.
Bold font indicates statistically significant results.

3.6 Factors contributing to the prevention of hypoparathyroidism after initial PTx

Univariate Cox regression analysis of the factors contributing to the prevention of hypoparathyroidism after PTx showed significant differences in dialysis vintage ($P < 0.001$; HR, 0.996; 95% CI, 0.995–0.998), preoperative vitamin D receptor activation therapy ($P = 0.008$; HR 0.748; 95% CI, 0.603–0.928), serum intact PTH levels at admission ($P = 0.009$; HR, 1.000; 95% CI, 1.000–1.000), maximum diameter of PTG for autograft ($P = 0.019$; HR, 1.033; 95% CI, 1.005–1.061), and weight of PTG for autograft ($P = 0.028$; HR, 1.000; 95% CI, 1.000–1.001) (Table 6). Multivariate Cox regression analysis demonstrated significant differences in dialysis vintage ($P < 0.001$; HR, 0.996; 95% CI, 0.995–0.998). However, no significant differences were identified in the maximum diameter ($P = 0.474$; HR, 1.015; 95% CI, 0.975–1.056) and weight of PTG for autograft ($P = 0.586$; HR, 1.000; 95% CI, 1.000–1.001) (Table 7).

3.7 Impact of hyperplastic pattern on the prevention of hypoparathyroidism after initial PTx

No significant differences were identified regarding the impact of the hyperplastic pattern of autografted PTGs on the prevention of hypoparathyroidism after initial PTx, both in the unadjusted ($P = 0.163$) and adjusted Cox regression analyses for dialysis vintage, maximum diameter of PTG, and weight of PTG, as well as preoperative vitamin D receptor activation therapy ($P = 0.485$) (Table 8).

3.8 ROC curve analysis for the optimal maximum diameter of PTG for autograft

ROC curve analysis for the optimal maximum diameter of PTG for autograft demonstrated that a maximum diameter of < 14.0 mm was the optimal cutoff to prevent re-PTx for graft-dependent SHPT (area under the curve, 0.628; 95% CI, 0.551–0.705) (Figure 2).

4 Discussion

To the best of our knowledge, this is the first study to investigate the factors contributing to re-PTx due to graft-dependent recurrent SHPT before the completion of initial PTx and prevention of hypoparathyroidism after initial PTx. The results showed that dialysis vintage and the maximum diameter of the PTG for autograft were significant contributors to re-PTx due to graft-dependent recurrent SHPT. However, the maximum diameter of the PTG for autograft was not a significant contributor toward preventing hypoparathyroidism after PTx. Furthermore, the pathological hyperplastic pattern of PTGs did not contribute to the re-PTx or prevention of hypoparathyroidism after initial PTx. The optimal maximum diameter of PTG for autograft to prevent graft-dependent recurrent SHPT was < 14.0 mm.

10.3389/fendo.2023.1175237

TABLE 2 Intraoperative and postoperative findings.

		Non-re-PTx group $n = 709$	Re-PTx group $n = 61$	P value	OR	95% CI	
Intraoperative results	Maximum diameter of PTG for autograft (mm), mean (SD)	11.8 (3.4)	13.2 (3.5)	**0.001**			
	Weight of PTG for autograft (mg), mean (SD)	333.8 (266.0)	414.9 (241.4)	< **0.001**			
	Number of fragmented parathyroid pieces for autograft, mean (SD)	29.2 (2.7)	29.7 (1.9)	0.087			
Postoperative results	Serum albumin level on POD 1 (g/dL), mean (SD)	3.6 (0.5)	3.5 (0.5)	0.131			
	Serum alkaline phosphatase level on POD 1 (U/L), mean (SD)	451.3 (428.4)	447.0 (357.8)	0.687			
	Serum calcium level on POD 1 (mg/dL), mean (SD)	10.0 (0.8)	10.2 (0.6)	0.726			
	Serum calcium level corrected by serum albumin level on POD 1 (mg/dL), mean (SD)	10.4 (0.9)	10.8 (0.8)	0.832			
	Serum phosphorus level on POD 1 (mg/dL), mean (SD)	6.2 (4.5)	6.6 (1.6)	**0.028**			
	Serum intact PTH levels on POD 1 (pg/mL), mean (SD)	14.2 (10.4)	19.3 (14.3)	**0.012**			
	Hyperplastic pattern of PTG			0.348			
	Diffuse hyperplasia, *n* (%)	76 (96.2)	3 (3.8)				
	Diffuse and nodular hyperplasia, *n* (%)	350 (91.4)	33 (8.6)				
	Nodular hyperplasia, *n* (%)	269 (92.1)	23 (7.9)				
	Thyroid papillary carcinoma diagnosed in the paraffin section, *n* (%)	35 (4.9)	4 (6.5)	0.580	1.351	0.464	3.937
	Parathyroid carcinoma diagnosed in the paraffin section, *n* (%)	0	0	NA			
	Serum intact PTH levels before re-PTx for graft-dependent SHPT (pg/mL), mean (SD)		459.4 (276.0)	NA			
	Serum intact PTH levels 1 day after re-PTx for graft-dependent SHPT (pg/mL), mean (SD)		132.7 (160.2)	NA			
	Re-PTx for recurrent SHPT in the neck or mediastinum, *n* (%)	10 (1.4%)	3 (4.9)	0.076			
	Postoperative calcium supplementation therapy, *n* (%)	709 (100.0)	61 (100.0)	> 0.999	NA	NA	NA
	Postoperative vitamin D receptor activation therapy, *n* (%)	709 (100.0)	61 (100.0)	> 0.999	NA	NA	NA
	Postoperative calcimimetics therapy, *n* (%)	52 (8.0)	30 (50.0)	< **0.001**	11.558	6.471	20.642
	Kidney transplantation after initial PTx, *n* (%)	33 (5.0)	3 (5.0)	> 0.999	1.000	0.297	3.362
	Hypoparathyroidism after initial PTx, *n* (%)	331 (46.7)	0	< **0.001**			
	Death during the observation period, *n* (%)	31 (4.4)	3 (4.9)	0.746	1.130	0.335	3.807
	Observation period (months), mean (SD)	58.7 (53.5)	68.3 (33.9)	**0.003**			

CI, confidence interval; NA, not accessed; OR, odds ratio; POD 1, postoperative day 1; PTGs, parathyroid glands; PTH, parathyroid hormone; PTx, parathyroidectomy; SD, standard deviation; SHPT, secondary hyperparathyroidism. Bold font indicates statistically significant results.

A previous study reported that PTG autografts with nodular hyperplastic patterns are associated with a higher probability of re-PTx than those with diffuse hyperplastic patterns (23). A maximum PTG diameter of ≥ 8 mm during preoperative ultrasonography is reported to be associated with a nodular hyperplastic pattern of PTGs (27). Thus, PTGs measuring ≥ 8 mm in diameter during preoperative ultrasonography should not be used for autografts. However, it should be noted that preoperative imaging studies may not accurately diagnose PTGs, as they may misdiagnose lymph nodes or parts of the thyroid gland as PTGs, and undetected PTGs are also common (19, 28). Therefore, PTGs for autografts should be selected during the surgery itself, although the hyperplastic pattern cannot be diagnosed during the short duration of the surgery. The present study investigated factors contributing to re-PTx due to graft-dependent SHPT in patients with autografted parathyroid fragments derived from only one resected PTG. These patients had successful initial total PTx and transcervical thymectomy, as defined by serum intact PTH level < 60 pg/mL on postoperative day 1. To better understand the impact of patient and autografted PTG characteristics, only patients who were autografted from one of the resected PTGs were selected. Furthermore, only patients with successful initial total PTx and transcervical thymectomy were selected to minimize the impact of persistent or recurrent SHPT in the neck or mediastinal area. Previously, serum intact PTH levels < 60 pg/mL on postoperative day 1 were demonstrated to be a significant predictive factor of successful PTx, although it has less

TABLE 3 Univariate Cox regression analysis for re-parathyroidectomy due to graft-dependent recurrent secondary hyperparathyroidism.

	P value	HR	95% CI	
Sex (male vs. female)	0.717	0.910	0.549	1.511
Age (years)	0.255	1.014	0.990	1.038
Height (cm)	0.924	1.001	0.974	1.030
Body weight (kg)	0.952	0.999	0.978	1.021
Body mass index (kg/m^2)	0.994	1.000	0.928	1.079
Diabetic nephropathy (vs non-diabetic nephropathy)	0.398	0.606	0.189	1.938
Dialysis vintage (months)	**0.007**	0.995	0.991	0.999
Preoperative vitamin D receptor activation therapy (vs non-preoperative vitamin D receptor activation therapy)	0.076	0.612	0.356	1.052
Preoperative calcimimetic therapy (vs non-preoperative calcimimetic therapy)	0.315	1.366	0.744	2.508
Preoperative serum alkaline phosphatase level (U/L)	0.949	1.000	0.999	1.001
Preoperative serum calcium level corrected by serum albumin level (mg/dL)	0.187	1.229	0.905	1.669
Preoperative serum phosphorus level (mg/dL)	0.481	1.012	0.979	1.047
Serum intact PTH levels at admission (pg/mL)	0.096	1.000	1.000	1.001
Maximum diameter of PTG for autograft (mm)	**0.002**	1.119	1.041	1.202
Weight of PTG for autograft (mg)	**0.024**	1.001	1.000	1.002
Number of fragmented parathyroid pieces for autograft	0.938	0.994	0.862	1.147

CI, confidence interval; HR, hazard ratio; PTG, parathyroid gland; PTH, parathyroid hormone. Bold font indicates statistically significant results.

than 100% accuracy, because persistent or recurrent SHPT in the neck or mediastinal area was identified in 13 (1.7%) patients, similar to previous reports (17, 18). Nonetheless, the incidence of persistent or recurrent SHPT was still markedly lower compared with that of other reports (5–30%), indicating the usefulness of postoperative serum intact PTH level as a predictor of SHPT persistence or recurrence (19, 29–31).

Our results indicate that the maximum diameter of the PTG for autograft is a significant factor that can cause re-PTx due to graft-dependent SHPT, while the weight of the PTG was not a causative factor. A previous study reported that nodular hyperplasia in autografted PTGs could be associated with re-PTx (23). The present study investigated the impact of hyperplastic patterns on the re-PTx due to graft-dependent SHPT with adjustment for

TABLE 4 Multivariate Cox regression analysis for re-parathyroidectomy due to graft-dependent recurrent secondary hyperparathyroidism.

	P value	HR	95% CI	
Dialysis vintage (months)	**0.010**	0.995	0.992	0.999
Maximum diameter of PTG for autograft (mm)	**0.046**	1.107	1.002	1.224
Weight of PTG for autograft (mg)	0.832	1.000	0.999	1.001

CI, confidence interval; HR, hazard ratio; PTG, parathyroid gland. Bold font indicates statistically significant results.

TABLE 5 Impact of hyperplastic pattern on re-parathyroidectomy due to graft-dependent recurrent secondary hyperparathyroidism.

	Re-PTx group	Non-re-PTx group	Unadjusted				Adjusted for dialysis vintage, maximum diameter of PTG, and weight of PTG			
	n = 59	*n* = 695	HR	95% CI		*P* value	HR	95% CI		*P* value
Diffuse hyperplasia, *n* (%)	3 (3.8)	76 (96.2)	ref			0.568	ref			0.732
Diffuse and nodular hyperplasia, *n* (%)	33 (8.6)	350 (91.4)	1.900	0.582	6.204	0.288	1.507	0.453	5.014	0.504
Nodular hyperplasia, *n* (%)	23 (7.9)	269 (92.1)	1.817	0.544	6.062	0.331	1.634	0.480	5.566	0.432

CI, confidence interval; HR, hazard ratio; PTG, parathyroid gland; PTx, parathyroidectomy; ref, reference.

TABLE 6 Univariate Cox regression analysis for the factors contributing to the prevention of hypoparathyroidism after initial parathyroidectomy.

	P value	HR	95% CI	
Sex (male vs. female)	0.077	0.844	0.699	1.019
Age (years)	0.658	1.002	0.994	1.010
Height (cm)	0.110	0.992	0.982	1.002
Body weight (kg)	0.288	0.996	0.988	1.004
Body mass index (kg/m^2)	0.785	0.996	0.971	1.023
Diabetic nephropathy (vs non-diabetic nephropathy)	0.651	0.927	0.667	1.288
Dialysis vintage (months)	**< 0.001**	0.996	0.995	0.998
Preoperative vitamin D receptor activation therapy (vs non-preoperative vitamin D receptor activation therapy)	**0.008**	0.748	0.603	0.928
Preoperative calcimimetic therapy (vs non-preoperative calcimimetic therapy)	0.925	1.010	0.820	1.244
Preoperative serum alkaline phosphatase level (U/L)	0.066	1.000	1.000	1.000
Preoperative serum calcium level corrected by serum albumin level (mg/dL)	0.973	0.998	0.898	1.109
Preoperative serum phosphorus level (mg/dL)	0.960	1.000	0.984	1.017
Serum intact PTH levels at admission (pg/mL)	**0.009**	1.000	1.000	1.000
Maximum diameter of PTG for autograft (mm)	**0.019**	1.033	1.005	1.061
Weight of PTG for autograft (mg)	**0.028**	1.000	1.000	1.001
Number of fragmented parathyroid pieces for autograft	0.261	0.979	0.943	1.016

CI, confidence interval; HR, hazard ratio; PTG, parathyroid gland; PTH, parathyroid hormone. Bold font indicates statistically significant results.

patients and PTG characteristics obtained before the operation's completion. However, in contrast to previously published data, our results did not reveal any correlation of the hyperplastic pattern with the incidence of re-PTx. One possible explanation for these disparate findings could be that in the previous study, the patients and PTG characteristics were not adjusted using multivariate analysis, and the hyperplastic patterns were only categorized into diffuse and nodular hyperplasia. Another study reported a progressive change in hyperplastic pattern from diffuse to nodular hyperplasia and the concomitant existence of both types of hyperplasia (26). In contrast, the current study classified hyperplastic patterns into three distinct categories: diffuse hyperplasia, concomitant diffuse and nodular hyperplasia, and nodular hyperplasia. Concomitant diffuse and nodular hyperplasia was identified in 50.7% (383 out of 754) of PTGs. However, it should be noted that the selection of PTGs for autograft was based on their similarity to the normal PTGs. This selection bias may contribute to the similar results observed in hyperplastic patterns for re-PTx. To completely eliminate this bias, a randomized clinical trial would be necessary. To investigate the PTG characteristics associated with graft-dependent SHPT, this study only included patients who received autografted parathyroid fragments from a single resected PTG. Our results indicate that PTGs selected for autografts should be smaller than a certain diameter. ROC curve analysis demonstrated that PTGs with a maximum diameter < 14 mm might be the most suitable for autografts.

The present study investigated the prevention of hypopara thyroidism after initial PTx, as it has serious consequences such as low bone turnover and ectopic calcification, which can lead to cardiac events (32, 33). However, except for the duration of dialysis treatment, no other significant factors contributing to the prevention of hypoparathyroidism were identified among the characteristics of PTGs examined. Previously, it has been reported that intact PTH levels might increase with an increase in the autografted number of PTGs following total thyroidectomy (34). Herein, 30 fragmented parathyroid pieces were autografted; however, the effect of the number of autografted parathyroid pieces on hypoparathyroidism after initial PTx could not be investigated. Additionally, the hyperplastic pattern of PTGs did

TABLE 7 Multivariate Cox regression analysis for the factors contributing to the prevention of hypoparathyroidism after initial parathyroidectomy.

	P value	HR	95% CI	
Dialysis vintage (months)	**< 0.001**	0.996	0.995	0.998
Maximum diameter of PTG for autograft (mm)	0.474	1.015	0.975	1.056
Weight of PTG for autograft (mg)	0.586	1.000	1.000	1.001
Serum intact PTH levels at admission (pg/mL)	0.055	1.000	1.000	1.000

CI, confidence interval; HR, hazard ratio; PTG, parathyroid gland. Bold font indicates statistically significant results.

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TABLE 8 Impact of hyperplastic pattern on the prevention of hypoparathyroidism after initial parathyroidectomy.

	Hypoparathyroidism after initial PTx	Non-hypoparathyroidism after initial PTx	Unadjusted				Adjusted for dialysis vintage, maximum diameter of PTG, weight of PTG, and preoperative vitamin D receptor activation therapy			
	n = 324	*n* = 429	HR	95% CI		*P* value	HR	95% CI		*P* value
Diffuse hyperplasia, *n* (%)	33 (10.2)	46 (10.7)	ref			0.163	ref			0.485
Diffuse and nodular hyperplasia, *n* (%)	151 (46.6)	232 (54.1)	1.059	0.771	1.453	0.724	1.065	0.766	1.481	0.709
Nodular hyperplasia, *n* (%)	140 (43.2)	151 (35.2)	0.868	0.623	1.207	0.399	0.936	0.661	1.324	0.708

CI, confidence interval; HR, hazard ratio; PTG, parathyroid gland; PTx, parathyroidectomy; ref, reference.

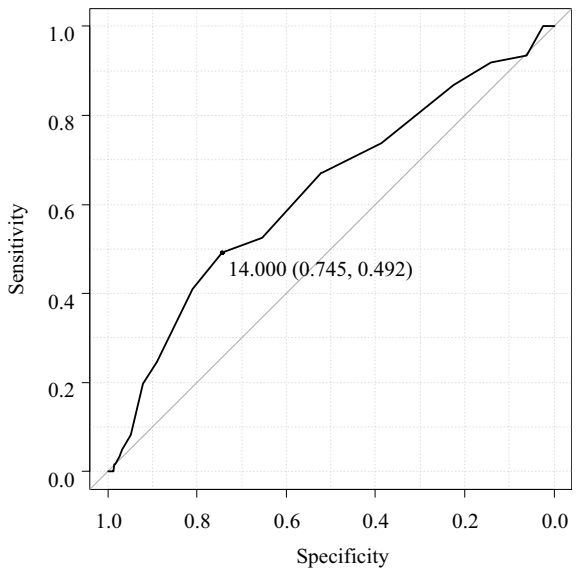

FIGURE 2
Receiver operating characteristic curve analysis for the optimal maximum diameter of the parathyroid gland for autograft.

not affect the incidence of hypoparathyroidism after initial PTx, suggesting that the hyperplastic pattern might not affect the function of the autografted parathyroid pieces.

The study has some limitations including its retrospective nature. Further, the impact of the number of autografted parathyroid pieces on hypoparathyroidism after initial PTx could not be investigated. The selection bias of PTGs for autograft could not be completely eliminated in this study, and future studies should adopt a prospective randomized approach to investigate the impact of autografted PTGs, including the number of autografted parathyroid pieces, on re-PTx and hypoparathyroidism.

In conclusion, the maximum diameter of the PTG for autograft is the factor contributing to re-PTx due to graft-dependent recurrent SHPT. PTGs with a maximum diameter of < 14 mm may be appropriate for autografts. These results may help surgeons to select optimal PTGs for autografts to prevent graft-dependent SHPT.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

TH designed and acquired the data, interpreted the results, and drafted the manuscript; MO acquired the data; YH, KF, NG, YT, SN, YW, and TI interpreted the results. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Improvement of hypertension control and left-ventricular function after cure of primary hyperparathyroidism

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Introduction: Cardiovascular mortality is significantly higher in patients with primary hyperparathyroidism (PHPT) compared to the general population. The role of the renin-angiotensin-aldosterone system (RAAS) as a mediator of cardiovascular pathology in PHPT is unclear, as is the question whether successful parathyroidectomy (PTX) mitigates hypertension (HT), and left-ventricular (LV) dysfunction.

Methods: In 45 consecutive, hypercalcemic PHPT patients (91% female, 20 normotensive, mean age 54.6 ± 14.6), laboratory examinations, and 24 h ambulatory blood pressure monitoring (ABPM) were performed before, one and six months after successful PTX, while transthoracic echocardiography (TTE) pre- and six months post-PTX.

Results: Both in patients with normotension (NT) and HT, lower calcemia and parathyroid hormone (PTH) as well as higher phosphatemia were observed on follow-up, while B-type natriuretic peptide, aldosterone, plasma renin activity, and aldosterone-to-renin ratios were comparable. Six months post-PTX, only in patients with HT, median 24-hour SBP/DBP decreased by 12/6 mmHg, daytime SBP by 10, and nighttime DBP by 5 mmHg. Improvement in BP was observed in approximately 78% of patients with HT. Six months post-PTX, TTE revealed: 1) decrease in median LV mass index (by 2 g/m2) and end-diastolic dimension (by 3 mm) among patients with HT; 2) normalization of global longitudinal strain in 22% of patients (comparable between those with NT and HT); 3) a mean 12.7% reduction in left-atrium volume index among patients with HT, which underlay normalization of indeterminate diastolic function in 3 out of 6 patients with HT, who exhibited it at baseline (dysfunction persisted in 2).

Conclusions: PTX was shown to significantly reduce BP, LV hypertrophy and diastolic dysfunction parameters in PHPT patients with HT, and improve systolic function in all PHPT patients.

KEYWORDS

global longitudinal strain, left ventricular dysfunction, primary hyperparathyroidism (pHPT), hypertension, aldosterone, parathyroidectomy

Introduction

Associations between primary hyperparathyroidism (PHPT) and cardiovascular (CV) diseases have not been studied extensively. Patients with PHPT are at an increased CV risk, and parathyroid hormone (PTH) has been postulated as an independent risk factor for CV diseases and sudden cardiac death (1, 2). CV diseases can be the main manifestation of both severe and mild or subclinical PHPT, yet, current endocrine guidelines do not account for hypertension (HT) or heart disease in the approach to management (3–6). Similarly, despite increased mortality due to CV diseases, PHPT is not discussed in cardiological guidelines.

HT is the most common CV complication of PHPT, and its prevalence is significantly higher in patients with this endocrinopathy than in the general population (7–9). Multiple mechanisms are involved in its pathogenesis, e.g. toxic effect of PTH on the vascular endothelium, dysfunction of vascular smooth muscles, vascular wall calcifications, and – possibly – stimulation of the renin-angiotensin-aldosterone system (RAAS) (8–16). Both elevated PTH and hypercalcemia affect the myocardium as well as vasculature. The former induces cardiac hypertrophy and positive chronotropic and inotropic effects (17–19). Hypercalcemia in the long-term leads to calcifications of the myocardium, valves and walls of vessels (18, 20). Elevated levels of PTH and calcium (Ca) are associated with higher arterial intima-media thickness (21–23). As a result, PTH increases the risk of myocardial ischemia and heart failure.

In the current study, we aimed at assessing the CV system in PHPT by investigating the effect of PTH and calcemia on blood pressure (BP), left-ventricular (LV) function as well as the RAAS in patients prior to and after successful parathyroidectomy (PTX).

Subjects and methods

Study participants and protocol

This study was approved by the local bioethics committee on July 2, 2015 (NKBBN/278/2015). Informed consent was obtained in writing from all study participants. Patients were recruited in the endocrine outpatient clinic of the Department of Endocrinology and Internal Medicine of the University Clinical Center of the Medical University of Gdańsk among those referred due to suspected or confirmed diagnosis of PHPT between 2015 and 2020.

The following inclusion criteria were adopted: age over 18, and diagnosis of PHPT based on the following laboratory criteria: serum PTH above 69 pg/mL (reference range 11–69) and total serum calcium (Ca) above 10 mg/dL (8.9–10). Exclusion criteria comprised: secondary and tertiary hyperparathyroidism, secondary HT, established or overt significant CV disease other than primary HT (in particular atherosclerotic CV disease including stroke, history of arterial revascularization, myocardial infarction, peripheral artery disease, as well as heart failure, clinically relevant valvular disease and arrhythmia), a lack of possibility of hypotensive therapy modification to medications non-interfering in the RAAS, active malignancy, poor physical condition, treatment with hypocalcemic drugs (e.g., biphosphates), albuminemia below 35 g/L, estimated glomerular filtration rate (eGFR) below 50 mL/min./1.73 m^2, absence of indication or lack of patient's consent for PTX.

In the period of the study, 45 patients were enrolled out of 85 referrals. PHPT was not confirmed in 21 patients (hyperparathyroidism was excluded in ten patients; eight and three were diagnosed with secondary and tertiary hyperparathyroidism, respectively), seven did not present for a follow-up visit, seven used biphosphates, three patients had contraindications to and two declined surgery.

The protocol consisted of: recording patient history and physical examination, additional examinations performed at baseline (prior to surgery), one and six months after successful surgical cure of PHPT. PHPT cure was defined as normal Ca along with normal or reduced by at least 50% PTH levels one month post-PTX. Laboratory tests and ambulatory blood pressure monitoring (ABPM) were performed before, ca. one and six months after successful surgical cure of PHPT, while transthoracic echocardiography (TTE) twice (before and six months after PTX). ABPM was conducted while patients were taking chronic hypotensive medications, after which a change to RAAS-non-interfering drugs (doxazosine and/or verapamil) for 14-18 days was made and laboratory tests were performed. In the case of examinations performed ca. one month post-PTX, ABPM was carried out between day 23 and 30, while laboratory assessment between day 37 and 45 after surgery. Directly (3-4 days) after ABPM, regular hypotensive drugs were re-introduced. Analogical assessment followed ca. 180 days post-PTX.

All patients had an enlarged parathyroid gland on sonography and/or scintigraphy. Histopathological diagnosis was mainly adenoma (63%), and less often hyperplasia. One female patient required two surgeries, since the first was unsuccessful.

Laboratory examinations

Blood was drawn from an upper extremity vein between 8 and 10 a.m., centrifuged for 10 minutes at 12000 rpms, after which serum and plasma were extracted and kept at -20 degrees C. Dry ice was used to transport frozen samples to the Central Diagnostic Laboratory of the same hospital, where concentrations of PTH, Ca, phosphate (P), aldosterone (Ald), B-type natriuretic peptide (BNP) and plasma renin activity (PRA) were determined. A Siemens IMMULITE 1000 Immunoassay System was used to measure serum PTH concentrations; Ca, P and BNP concentrations were measured with an Abbott Architect analyzer (spectrophotometric method). Ald concentrations and PRA were determined by immunochemiluminescence using DiaSorin assays. Reference ranges recommended by manufacturers were adopted as normal. Ald-to-PRA ratio (ARR) below 30 ng/dL: ng/mL/h was considered normal.

Office and ambulatory blood pressure measurements

The non-dominant arm was chosen for BP measurements. Office BP was measured using a validated device by Omron. Three measurements at one minute intervals were performed on

every visit, and the mean of the second and third measurement was recorded. In-office BP was categorized in accordance with the ESC/ESH 2018 guideline as: optimal for measurements <120/80 mmHg, high normal for SBP 120-130 and/or DBP 80-84 mm, high normal for SBP of 130-139 and/or DBP of 85-89 mmHg, grade 1 for SBP 140-159 and/or DBP 90-99 mmHg, grade 2 for SBP 160-179 and/or DBP 100-109 mmHg, and grade 3 for SBP ≥180 and/or DBP ≥110 mmHg (24).

ABPM was conducted for at least 24 hours using a Spacelabs Ontrak 90227 monitor. Measurements were made every 15–20 minutes during daytime, and every 30 minutes at night. An arbitrary period between 10 p.m. and 6 a.m. was chosen for nighttime rest, and patients were obligated to follow it. If more than 30% of measurements were invalid, ABPM was repeated. ABPM results included mean 24-h, diurnal and nocturnal SBP and DBP as well as dipping status (normal provided mean nocturnal SBP and DBP were at least 10% lower than mean daytime readings). Normal SBP/DBP mean values acquired by ABPM were adopted from the 2018 ESC/ESH guideline: below 130/80 mmHg for the 24 h, below 135/85 mmHg for daytime, and below 120/70 mmHg for nighttime periods.

In follow-up assessment one and six months after surgery, improvement in BP was stated based on office and ambulatory measurements versus pre-PTX results if either of the following occurred: 1) cure of HT (office BP<140/90 mmHg, and normal mean SBP/DBP in ABPM without hypotensive medications), 2) better HT control, i.e., normalization of elevated pre-PTX 24-h, daytime and/or nighttime SBP/DBP with the same or lower number of hypotensive drugs, 3) comparable/lower 24-h, day- and/or nighttime SBP/DBP with fewer hypotensive drugs, and 4) dipping profile normalization.

Echocardiography

Examinations were carried out on a GE Vivid E95 4D cardiovascular ultrasound machine in accordance with the Polish Society of Cardiology guidelines [24], [25]. Images were obtained typically in the parasternal long and short axis as well as apical, two-, three- and four-chamber projections. The following parameters were acquired: diastolic thickness of the interventricular septum (IVS), left ventricular end-diastolic dimension (LVEDd), left ventricular end-systolic dimension (LVESd), posterior wall thickness (PW), left-ventricular ejection fraction (LVEF), left atrial diameter (LAd), left atrial volume (LAV), left atrial volume index (LAVI), relative wall thickness (RWT), left ventricular mass (LVM), left ventricular mass index (LVMI), global longitudinal strain (GLS) and LV diastolic function parameters. RWT was calculated from the formula: RWT=2×PW/LVEDd.

We used the area-length method to calculate LVM. Measurements were performed at the end of diastole. Mean wall thickness was calculated from epicardial and endocardial cross-sectional areas in short-axis view at the papillary muscle level. LV mass was calculated from these measurements and LV length measured from the base to the apex. LVMI was indexed to body surface area (BSA) obtained from the Du Bois formula (BSA=0.007184 × W0.425 × H0.725, where W denotes body weight in kilograms, and H – height in meters): LVMI=LVM/BSA.

LAV was calculated by disk summation technique (modified biplane) from apical four and two chamber views. LAV was indexed to BSA (LAVI=LAV/BSA).

Four criteria for diastolic function assessment in patients with normal LVEF (>52% in men, >54% in women): 1) LAVI >34 mL/m^2, 2) tricuspid regurgitation velocity (TR) >2.8 m/s, 3) early diastolic transmitral flow velocity (E)-to-averaged early diastolic mitral annular velocity (e') ratio above 14 (E/e'>14), and 4) septal e'<7 cm/s or lateral e'<10 cm/s. In women with LVEF<55%, E was >50 cm/s and E-to-late diastolic peak velocity flow (A) ratio (or E/A) was below 2, therefore, three diastolic dysfunction criteria were assessed: E/e'>14, LAVI>34 mL/m^2, TR>2.8 m/s [25].

GLS was measured by tracking acoustic markers in 3 standard projections (apical four-chamber, two-chamber, and long axis), and mean value was recorded. GLS was obtained from the formula: GLS (%)=100%×(MLs-MLd)/MLd, where MLs denotes myocardial length at late LV systole, and MLd – myocardial length at end-diastole. GLS above -19.5% (closer to zero) was considered abnormal.

Statistical analysis

Statistical calculations were performed using GraphPad Prism software with one exception. Selection of statistical tools depended on the distribution of data. Kolmogorov-Smirnov test was used to test the normalcy of distribution. If normal, Student's t-test was used for comparisons of two groups and repeated measures ANOVA with post-hoc Tukey's test for paired data from three examination timepoints. To test data with non-normal distributions, U Mann-Whitney and Friedman's (with *post hoc* Dunn's multiple comparison) tests were used. Correlations were assessed using Pearson's and Spearman's methods depending on the distribution; their significance was verified with a dedicated test. Statistica version 14 software was applied to verify differences in binary variables at three examination timepoints by Cochran's q test. Differences between two groups in binary variables were verified with Fisher's exact test. Results are reported as number (%), arithmetic mean ± standard deviation (SD), and median (interquartile range, IQR). Significance was set at <0.05.

Results

Clinical data of study participants

Patients were predominantly female (41 versus 4), aged 54.6 ± 14.6 (range 25-80 years), with a mean BMI of 25.4 ± 5.2. Duration of PHPT based on anamnesis was 3.8 ± 2.8 years, its complications included nephrolithiasis in 29%, osteopenia in 18%, and osteoporosis in 33% of patients. Type 2 diabetes was present in 16 patients (36%), and hypercholesterolemia in 23 (51%); fifteen were active smokers.

Before enrollment, HT had been diagnosed in 22 patients (3.2 ± 1.8 years earlier – comparable to the time of PHPT diagnosis), while

in 3 it was newly diagnosed based on office measurements and ABPM. A trend toward longer PHPT duration in patients with HT than NT could be observed (4.4 ± 2.7 versus 3.1 ± 1.7 years, p=0.06). Among the former, seven were aged below 50, eleven between 50 and 65, and seven 65 or older. Mean BMI of hypertensive patients was higher than that of normotensive: 26.9 ± 4.6 kg/m^2 versus 23.5 ± 5.3, p=0.03, while mean age was similar (57 ± 13 vs 51 ± 16).

Effect of parathyroidectomy on laboratory parameters

In one patient, calcemia equal to 10.9 mg/dL six months post-PTX resulted from iatrogenic calcium and alfa-calcidiol treatment and was fixed at 10 mg/dL. Two PRA values with corresponding ARRs were excluded from analysis due to a probable pre-laboratory error: 0.01 ng/mL/h pre-PTX in one participant, and 0.09 ng/mL/h one month post-PTX in another (both hypertensive females).

Prior to PTX, all patients met laboratory criteria for PHPT. After PTX, PTH and Ca decreased, while P increased significantly both in subjects with NT and HT (Table 1). Concerning RAAS parameters, there were three, three and four patients with an ARR>30, respectively, prior to, one and six months after surgery. However, in these patients, Ald and PRA values did not consistently indicate primary aldosteronism, i.e., at least at one point Ald was lower than 8 ng/dL and/or PRA exceeded 1 ng/mL/h. In contrast to calcium-phosphate parameters, initial BNP, Ald, PRA and ARR did not differ significantly from those on follow-up (Table 1).

Prior to PTX, there were statistically significant Pearson's correlations between: PTH and Ca (R=0.54, p<0.0005), PTH and P (R=-0.42, p<0.005), Ca and P (R=-0.34, p=0.02). Neither before, nor after PTX were significant correlations found between Ca, PTH or P and BNP, Ald, PRA or ARR.

Pre-PTX, differences in Ald, PRA, ARR, and BNP were not found between patients in the lower half of Ca concentrations (<11.6 mg/dL) and others, nor between those with PTH lower than the median (144 pg/mL) and others.

P articipants with normotension (NT) had higher baseline calcium (11.9 ± 0.9 vs 11.3 ± 0.9 mg/dL, p=0.035), lower baseline and 6-month-post-PTX BNP, and a higher reduction in PTH one month post-PTX (150 ± 126 vs 80 ± 59 pg/mL, p=0.02) and Ca six month post-PTX (2.4 ± 0.9 vs 1.7 ± 0.9 mg/dL, p=0.01) than patients with HT (Table 1). These groups did not differ in Ald, PRA and ARR.

Among 20 patients with NT, no baseline correlations were found between Ca, P, PTH and Ald, PRA or ARR. There were also no statistically significant differences between pre- and post-PTX Ald, PRA and ARRs, nor a clear trend toward higher or lower levels. Similarly, in 25 patients with HT, no correlations were recorded between Ca, P or PTH and Ald, PRA or ARR, nor a trend hinting at possible differences (pre-surgery values were not significantly different from post-surgery ones, Table 1).

Finally, laboratory data were analyzed in hypertensive patients with and without BP improvement one month post-PTX (n=18 and 7, respectively). Baseline PTH was higher in those without improvement (180 ± 62 versus 125.3 ± 55.8 pg/mL, p=0.04). Among patients with HT and BP improvement, no trend was observed toward lower Ald or ARR, nor statistical significance upon testing for: a) differences in Ald, PRA and ARR at the three timepoints, b) correlations between Ald, PRA or ARR and Ca, P or PTH, nor c) correlations between pre- to post-surgery changes in RAAS and Ca-P parameters.

Effect of parathyroidectomy on blood pressure

Overall, median daytime DBP was 5 mmHg lower one month post-PTX, and median 24-h SBP 9 mmHg lower six months post-PTX compared to baseline (Table 2). In patients with NT, ABPM

TABLE 1 Laboratory parameters before and after PTX.

	All patients (n=45)				Patients with NT (n=20)				Patients with HT (n=25)			
	pre-PTX	1 and 6 months post-PTX		p	pre-PTX	1 and 6 months post-PTX		p	pre-PTX	1 and 6 months post-PTX		p
Ca [8.9-10 mg/dL]	11.5 ± 0.9	9.6 ± 0.6	9.5 ± 0.4	<10^{-4}	11.9 ± 0.8	9.6 ± 0.6	9.4 ± 0.4	<10^{-4}	11.3 ± 0.9*	9.6 ± 0.5	9.6 ± 0.4	<10^{-4}
P [2.3-4.7 mg/dL]	2.2 ± 0.2	3 ± 0.6	3.1 ± 0.6	<10^{-4}	2.2 ± 0.2	3 ± 0.4	3.1 ± 0.5	<10^{-4}	2.2 ± 0.8	3 ± 0.7	3.2 ± 0.7	<10^{-4}
PTH [10-69 pg/mL]	144 (91)	48.7 (41.1)	34.8 (27.1)	<10^{-4}	192.2 ± 128.9	41.75 ± 22	36 ± 17.3	<10^{-4}	140.6 ± 61.6	60.4 ± 42.2	42 ± 23	<10^{-4}
BNP [<150 pg/mL]	16 (26.5)	17 (22.5)	18 (35.5)	n.s.	12.5 (15)	16.5 (17.3)	13 (14.8)	n.s.	27 (31.5)$^{\#}$	18 (24)	25 (44.3)$^{\#\#}$	n.s.
Ald [4.4-46.1 ng/dL]	10.5 (7.2)	10.5 (5.9)	9.5 (4.5)	n.s.	11.2 ± 5.5	10.6 ± 5.8	10.6 ± 5.4	n.s.	8.8 (8.1)	10.7 (7)	9.9 (6.2)	n.s.
PRA [ng/mL/h]	1.4 (1.6)	1.2 (1.7)	1.3 (2.2)	n.s.	1.4 (1.7)	1.2 (1.9)	1.3 (2.4)	n.s.	1.6 (5.1)	1.3 (3.2)	1.2 (3)	n.s.
ARR [<30]	6.5 (9)	8 (8.7)	7.2 (10.6)	n.s.	8.9 (6)	9.2 (7.7)	8.1 (6.8)	n.s.	4.1 (10.1)	6.9 (7.5)	6.3 (13.3)	n.s.

Data are presented as mean ± SD or median (interquartile range); p is given for repeated measures ANOVA or Friedman's test results; * pre-PTX, mean Ca was higher in patients with NT than HT (p=0.03, t Student test); # and ## pre- and 6 months post-PTX, median BNP was higher in patients with HT than NT (p=0.037 and 0.041, Mann-Whitney U test); n.s., not significant; PTX, parathyroidectomy.

10.3389/fendo.2023.1163877

results did not change post-PTX, whereas in patients with HT the following decreased significantly six months after surgery: 24-h SBP and DBP, daytime SBP, and nighttime DBP (Table 2). Mean change in 24-h, diurnal and nocturnal SBP as well as nighttime DBP from pre- to six-month-post-PTX values differed between patients with NT and HT (p between 0.01 and 0.04).

Regarding associations between BP and laboratory data, in all patients, the higher the decrease in PTH one month after PTX was, the lower 24-h, daytime SBP, DBP and nighttime DBP were (Pearson's R between -0.43 and -0.35, p between 0.003 and 0.03). There were no correlations between ABPM and laboratory data in patients with NT and HT analyzed separately.

Among 25 patients with HT, there were 7 and 5 without improvement in BP, respectively one and six months after PTX, while in others the improvement consisted in: 1) cure of HT in 3 and 5 patients (1 with newly diagnosed HT), 2) better HT control (normalization of 24-h, day- and/or nighttime SBP/DBP) in 13 and 14 patients, 3) treatment with fewer hypotensive medications without an increase in BP in 7 and 9 patients, 4) change to dipper in 9 and 7 patients, respectively one month and six months post-PTX (Table 3). Taken together, improvement occurred in 18 patients (76%) one month, and 20 (80%) six months after surgery. Several patients met more than one criterion of BP improvement (e.g. 7 required fewer drugs to achieve better HT control).

Lastly, data of hypertensive patients with (n=18) and without (n=7) improvement in BP one month after PTX were analyzed. While pre-PTX, the former had higher 24-h SBP (146.2 ± 20.7 vs 125.7± 19.5 mmHg, p=0.03), nighttime SBP (134 ± 19.1 vs 114.3 ± 22.8 mmHg, p=0.04) and DBP (79.4 ± 13.8 vs 65.4± 18.4 mmHg, p<0.05), both one month and six months post-PTX 24-h, daytime SBP and nighttime SBP/DBP decreased by 10.8 to 22.6 mmHg in the former, while did not change significantly in the latter.

Effect of parathyroidectomy on echocardiographic parameters

Considering all patients, LVEDd, LVM and LVMI decreased after PTX, which was attributable to those with HT (Table 4).

There was no statistically significant change in LVEF in patients with NT nor with HT. Reduced LVEF was recorded in four women pre-PTX (45%, 45%, 50%, and 52%), and remained so in two post-PTX (48%, 50%, 57%, and 58%, respectively).

Before surgery, normal (below -19.5%) GLS was recorded in 17 patients (37.8%), which improved to 60% six months post-PTX. In

TABLE 2 Blood Pressure in 24-hour ambulatory monitoring before and after PTX.

	pre-PTX	1 month post-PTX	6 months post-PTX	p
All patients (n=45)				
24-h SBP	129 (21.5)	124 (19.5)	**120 (12)**	0.024[a]
24-h DBP	76 (17.5)	75 (12.5)	73 (12)	0.09
Daytime SBP	133 (22)	128 (20)	123 (14.5)	0.055
Daytime DBP	83 (19.5)	**78 (14)**	77 (12)	0.015[b]
Nighttime SBP	117 (29)	109 (19)	107 (13)	0.356
Nighttime DBP	67 (20)	67 (16)	65 (13)	0.156
Dipper status	27 (60%)	41 (91%)	41 (91%)	0.38
Patients with NT (n=20)				
24-h SBP	119.9 ± 13	118.2 ± 13.8	118.2 ± 10.9	0.54
24-h DBP	72.9 ± 10.4	71.35 ± 9.8	71.6 ± 8.9	0.92
Dipper status	12/16 (75%)	8/15 (53.3%)	11/15 (73.3%)	0.31
Patients with HT (n=25)				
24-h SBP	135 (33)	131 (17)	**123 (13)**	0.014[c]
24-h DBP	80 (24)	76 (12)	**74 (11.5)**	0.034[d]
Daytime SBP	138 (40)	135 (17)	**128 (13)**	0.042[e]
Daytime DBP	85 (27)	80 (10.5)	78 (11)	0.08
Nighttime SBP	129 (23)	118 (23)	109 (16)	0.31
Nighttime DBP	71 (28)	68 (12)	**66 (11.5)**	0.02[f]
Dipper status [n (%)]	16 (64%)	12 (48%)	16 (64%)	0.33

Data are presented as mean ± SD, median (IQR) or n(%); bold font indicates post-PTX values significantly different from pre-PTX; p for Friedman or repeated measures ANOVA test; superscript letters are used to indicate the following p in Dunn's multiple post-hoc test: a and b – 0.034; c – 0.018; d – 0.049, e – 0.04, f – 0.022; HT – hypertension; NT – normotension; PTX – parathyroidectomy.

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TABLE 3 Change in blood Pressure in hypertensive patients after PTX.

Patients with HT (n=25)	1 month post-PTX	6 months post-PTX
Improvement in BP control	18 (72%)	20 (80%)
Cure of HT	3 (12%)	5 (20%)
Better HT control	13 (52%)	14 (56%)
Fewer drugs without higher BP	9 (36%)	6 (24%)
Change to dipper	3 (12%)	7 (28%)
No improvement in BP control	7 (28%)	5 (20%)
Change to non-dipper	7 (28%)	3 (12%)

Data are presented as n (%) and indicate change versus pre-PTX results, BP, blood pressure; HT, hypertension; PTX, parathyroidectomy.

contrast to hypertrophy parameters, GLS was lower (better) in patients with NT after surgery, but not in those with HT. Still, also in the latter normal GLS following PTX was recorded more frequently (Table 4).

Concerning diastolic function, it was normal in patients with NT at both timepoints, while a 12.7% reduction in LAVI was observed post-PTX in patients with HT. A trend toward fewer instances of indeterminate diastolic function after surgery (6 versus 3) could be observed in the latter, while diastolic dysfunction persisted in 2 (Table 4).

No significant correlations were found between laboratory and echocardiographic parameters. Ald and ARR decreased and increased in a similar number of patients, therefore, correlations with TTE parameters were not tested.

In subjects with HT, baseline PTH correlated with IVS (Spearman's r=0.6, p=0.002) and PW (r=0.48, p=0.016). Upon analyzing 18 hypertensive patients with improvement in BP one month post-PTX, no statistically significant correlations between changes in laboratory and echocardiographic parameters were found; however, LVM and LVMI correlated with changes in 24-h and daytime SBP and DBP (Spearman's r between 0.44 and 0.57, p between 0.014 and 0.046).

Discussion

Our data indicate that surgical cure of PHPT reduces BP and LV hypertrophy among hypertensive patients, as well as improves cardiac function both in normo-, and – more markedly – in hypertensive patients, independently of the RAAS. BNP remained higher in patients with HT than with NT, which is probably attributable to higher LAVI in the former. Strong points of our study include a clearly defined patient population, careful preparation, and thorough evaluation of patients (clinical, laboratory, ABPM, and TTE assessment). Limitations include lack of controls, small sample size considering wide range of age, patient heterogeneity as well as a rather short follow-up period.

TABLE 4 Echocardiographic parameters before and six months after PTX.

	All patients (n=45)			Patients with NT (n=20)			Patients with HT (n=25)		
	pre-PTX	post-PTX	p	pre-PTX	post-PTX	p	pre-PTX	post-PTX	p
IVS [mm]	10 (3)	10 (3)	n.s	9.5 (2.8)	9 (2.5)	n.s	10 (2) *	10 (2) **	n.s
LVEDd [mm]	45 (6)	42 (3.5)	0.014	43.1 ± 5.1	42.8 ± 4.2	n.s	45 (7.5)	42 (7)	0.023
LVESd [mm]	29.2 ± 5.9	29.3 ± 5.3	n.s.	28.6 ± 3.9	29.4 ± 3	n.s	29.8 ± 7.2	29.3 ± 6.6	n.s
PW [mm]	9 (2)	9 (2)	n.s	9 (1)	8.5 (1)	n.s	10 (2) *	10 (1) **	n.s
LAd [mm]	35 (9)	34 (9)	n.s	32 ± 5.2	32.6 ± 4.6	n.s	38.2 ± 5.9 *	37.6 ± 6.2 **	n.s
LAV [ml]	49.1 ± 19.2	46.1 ± 14.9	n.s	37.7 ± 10.2	39.8 ± 11.3	n.s	58.3 ± 19.9*	51.1 ± 15.6**	0.036
LAVI [ml/m²]	27.9 ± 11.5	25.8 ± 7.8	n.s.	21.8 ± 5.9	22.4 ± 5.9	n.s.	32.8 ± 12.6*	28.6 ± 8 **	0.043
Normal diast. function [n(%)]	37(82.2%)	40(88.9%)	n.s	20 (100%)	20 (100%)	n.s.	17(68%) *	20 (80%)	n.s.
LVEF [%]	58 (6)	59 (4)	n.s	58 ± 3.2	58.2 ± 2.7	n.s	59 ± 7.1	59.7 ± 6.9	n.s
LVM [g]	109 (50)	103 (40)	$<10^{-3}$	103 (33)	101 (50)	n.s	117 (49)	104 (31)	10^{-3}
LVMI [g/m²]	63.3(19.5)	61.2 (14.1)	10^{-3}	63.5 ± 11.6	63.6 ± 12.9	n.s	63.6 (22.4)	60.2 (11.8)	10^{-3}
E/e`	9.13 ± 2.76	9.1 ± 2.44	n.s	8.78 ± 2.5	8.6 ± 2.3	n.s.	9.41 ± 2.97	9.5 ± 2.52	n.s.
RWT [mm]	0.44 ± 0.09	0.45 ± 0.1	n.s	0.42 ± 0.1	0.41 ± 0.08	n.s	0.46 ± 0.08	0.48 ± 0.1	n.s
GLS [%]	-19 (3.5)	-20 (2)	<0.01	-18.5 (2)	-20 (2)	<0.01	-19 (4)	-20 (2.5)	n.s
Normal GLS [n(%)]	17 (38%)	27 (60%)	10^{-3}	8 (40%)	13 (65%)	0.02	9 (36%)	14 (56%)	0.02

mean ± SD, median(IQR) or n(%) are presented; * and ** denote statistically significant differences between patients with NT and HT, respectively pre- and post-PTX, p between 0.0004 and 0.007; diast., diastolic; GLS, global longitudinal strain; GLS was considered normal when equal to or lower (more negative) than -19.5%; HT, hypertension; n.s., not significant; NT, normotension; PTX, parathyroidectomy.

Thus far, discordant findings have been reported concerning the reversibility of HT or BP reduction following the cure of PHPT. Ejlsmark-Svensson et al. compared PHPT patients randomized to observation (n=36) or surgery (n=33), and found BP did not change three months after PTX in the latter (25). In a larger, randomized controlled trial, two years post-PTX, a decrease in DBP and mean BP was observed in operated (n=54) but not observed (n=62) patients, however, with no significant difference between these groups (26). Unchanged BP values were also recorded after surgery in two small observational studies (n=48 and 30, respectively) by Karakose et al. and Nilsson et al. (14, 27). In these four studies, patients with NT and HT were not analyzed separately, which is vital, since the effect of PTX on BP was apparent only in the latter in several other reports. This is indicated by findings from a large retrospective cohort (n=1020) and a smaller one (n=368): six months post-PTX, SBP and DBP decreased in patients with HT (71% and 50%, respectively) but not those with NT (28, 29). Our data also point at the beneficial effect of surgery on BP in hypertensive patients only. However, there are reports with contrasting results. For instance, Rydberg et al. observed 5 mmHg higher SBP in 20 PHPT patients with HT after PTX, yet, they were older, PHPT and HT had lasted longer, and hypercalcemia was milder than in our patients. In turn, Beysel et al. reported a BP reduction in both 35 normo- and 60 hypercalcemic patients (43% and 63% with HT, respectively) six months after successful surgery (13, 30).

Similarly to data concerning BP, improvement in echocardiographic parameters after PTX recorded in our study (LVH reduction, better systolic and diastolic function) can only be partially tracked to previous studies. In particular, at the same six-month follow-up: Agarwal et al. found LVEF and diastolic function (E/A ratio) improved, Kepez et al. reported better LV contractility by speckle tracking examination but no change in LVM or diastolic function, while in patients randomized to surgery (n=12) or observation (n=12) by Pepe et al. neither systolic nor diastolic cardiac function altered (31–33). Two meta-analyses (from 2015 and 2017) contain discordant findings: a decrease in LVM was reported by McMahon et al. in short-term follow-up (up to 6 months) based on 15 prospective studies (11 observational, 4 randomized, n=457), while Best and colleagues found no differences in LVEF or IVS, RWT, and two diastolic function parameters upon analyzing 14 studies (3 randomized, n=424) (34, 35). Heterogeneity of the designs and patient populations (in particular concerning CV risk factors and PHPT severity) probably account for divergent results. It is worth noting that in our study a decrease in LVM and LAVI was recorded in hypertensive, while GLS improved more markedly in normotensive patients.

PTH excess present in PHPT has been implicated as a stimulatory factor for the RAAS. In particular, several studies documented lower Ald, PRA and/or angiotensin II after PTX (36). The current study does not confirm this: neither before nor after PTX were there significant abnormalities in the RAAS parameters, and no change was recorded in Ald, PRA and ARR in patients with NT nor HT following surgery. Similar findings were reported by Bernini et al., and Salahudeen et al., as well as Castellano et al. in normotensive PHPT patients (37–39). Multiple factors affecting the RAAS significantly complicate investigations of possible relationships with calcium-phosphate parameters, e.g. patient populations, medications (especially hypotensive drugs), age, presence of HT, hydration, laboratory assays, etc. Mild primary aldosteronism concomitant with PHPT should also be taken into consideration in light of partly similar demographic (age above 50) (40).

Conclusions

PHPT is nowadays rarely diagnosed in patients with classic symptoms, hence, data on HT and impaired cardiac function due to this endocrinopathy gain importance. In our study, normotensive patients with PHPT had comparable ABPM results but better systolic function post-PTX, while those with HT exhibited lower BP and LV hypertrophy parameters, improved systolic and diastolic function on follow-up. These significant cardiovascular benefits of surgical cure of PHPT require further confirmation in larger studies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Independent Bioethics Committee for Research of the Medical University of Gdańsk. The patients/participants provided their written informed consent to participate in this study.

Author contributions

IK, KS and SK-J contributed to conception and design of the study. IK, SK-J, KS, IP and MF contributed to data acquisition. IK and PK organized the database. PK performed the statistical analysis. IK and PK wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cinacalcet use in secondary hyperparathyroidism: a machine learning-based systematic review

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Introduction: This study aimed to systematically review research on cinacalcet and secondary hyperparathyroidism (SHPT) using machine learning-based statistical analyses.

Methods: Publications indexed in the Web of Science Core Collection database on Cinacalcet and SHPT published between 2000 and 2022 were retrieved. The R package "Bibliometrix," VOSviewer, CiteSpace, meta, and latent Dirichlet allocation (LDA) in Python were used to generate bibliometric and meta-analytical results.

Results: A total of 959 articles were included in our bibliometric analysis. In total, 3753 scholars from 54 countries contributed to this field of research. The United States, Japan, and China were found to be among the three most productive countries worldwide. Three Japanese institutions (Showa University, Tokai University, and Kobe University) published the most articles on Cinacalcet and SHPT. Fukagawa, M.; Chertow, G.M.; Goodman W.G. were the three authors who published the most articles in this field. Most articles were published in *Nephrology Dialysis Transplantation*, *Kidney International*, and *Therapeutic Apheresis and Dialysis*. Research on Cinacalcet and SHPT has mainly included three topics: 1) comparative effects of various treatments, 2) the safety and efficacy of cinacalcet, and 3) fibroblast growth factor-23 (FGF-23). Integrated treatments, cinacalcet use in pediatric chronic kidney disease, and new therapeutic targets are emerging research hotspots. Through a meta-analysis, we confirmed the effects of Cinacalcet on reducing serum PTH (*SMD* = -0.56, 95% *CI* = -0.76 to -0.37, p = 0.001) and calcium (*SMD* = -0.93, 95% *CI* = -1.21to -0.64, p = 0.001) and improving phosphate (*SMD* = 0.17, 95% *CI* = -0.33 to -0.01, p = 0.033) and calcium-phosphate product levels (*SMD* = -0.49, 95% *CI* = -0.71 to -0.28, p = 0.001); we found no difference in all-cause mortality (*RR* = 0.97, 95% *CI* = 0.90 to 1.05, p = 0.47), cardiovascular mortality (*RR* = 0.69, 95% *CI* = 0.36 to 1.31, p = 0.25), and parathyroidectomy (*RR* = 0.36, 95% *CI* = 0.09 to 1.35, p = 0.13) between the Cinacalcet and non-Cinacalcet users. Moreover, Cinacalcet was associated with an increased risk of nausea (*RR* = 2.29, 95% *CI* = 1.73 to 3.05, p = 0.001), hypocalcemia (*RR* = 4.05, 95% *CI* = 2.33 to 7.04, p = 0.001), and vomiting (*RR* = 1.90, 95% *CI* = 1.70 to 2.11, p = 0.001).

Discussion: The number of publications indexed to Cinacalcet and SHPT has increased rapidly over the past 22 years. Literature distribution, research topics, and emerging trends in publications on Cinacalcet and SHPT were analyzed using a machine learning-based bibliometric review. The findings of this meta-

analysis provide valuable insights into the efficacy and safety of cinacalcet for the treatment of SHPT, which will be of interest to both clinical and researchers.

KEYWORDS

calcimimetics, FGF-23, bibliometrics, LDA analysis, machine learning

1 Introduction

Secondary hyperparathyroidism (SHPT) is a medical condition in which a systemic condition outside the parathyroid glands causes all parathyroid glands to become enlarged and hyperactive (1). The most common cause of SHPT is chronic kidney disease (CKD; i.e., a kidney disorder in which a gradual loss of kidney function occurs over a period of months to years; 2). With CKD progression, the kidneys can no longer maintain a calcium and phosphate balance; such changes signal the parathyroid glands to produce excessive amounts of parathyroid hormone (PTH) and grow larger, causing SHPT (3). SHPT is significantly associated with cardiovascular mortality and all-cause mortality (4). Currently, the main treatments for managing SHPT include parathyroidectomy, phosphate binders (i.e., medications used to reduce the absorption of dietary phosphate; 5), vitamin D supplements, and calcimimetics (i.e., drugs that mimic the action of calcium on tissues; 6). Parathyroidectomy, the conventional therapy, is generally a safe procedure; however, as surgery does not treat the disease that causes SHPT, there is a high chance of recurrence; therefore, surgery is not the best option for treating SHPT. If symptoms persist after nonsurgical treatment, a parathyroidectomy may be advised (7). Compared to other treatments, calcimimetics are new but since they play an irreplaceable role in reducing the levels of PTH and serum calcium, calcimimetics are the most widely used treatment strategy for SHPT (8). The *Kidney Disease: Improving Global Outcomes* (KDIGO) guidelines have identified calcimimetics as the first-line therapy for SHPT (9).

Cinacalcet was the first calcimimetic drug to be approved by the United States (U.S.) Food and Drug Administration (10). Cinacalcet is safe and effective in clinical trials, demonstrating superior efficacy in improving bone histology and vascular calcification (11, 12). The advent of cinacalcet has effectively reduced the need for parathyroidectomy (13, 14). Although side effects (e.g., hypocalcemia, nausea, and vomiting) and severe adverse events (e.g., mortality and cardiovascular events) have been reported, the FDA has recently approved more calcimimetics (e.g., Etelcalcetide and Evocalcet) for the treatment of SHPT (15), cinacalcet remains the most prescribed calcimimetic drug (16–18).

Systematic reviews are used to synthesize and criticallyevaluate research findings on a specific topic and are particularly important in the field of medicine to provide evidence-based information that can inform clinical decision-making. Bibliometric analysis, a tool used in systematic reviews, adopts mathematical and statistical methods to demonstrate knowledge structures and dynamic evolution of a specific research area (19). A significant amount of research has been conducted using bibliometric methods (e.g., 20–22). Another classical tool used in systematic reviews is meta-analysis, which combines data from multiple studies to obtain a more precise estimate of treatment effects. By synthesizing the results of multiple studies, a meta-analysis can provide a comprehensive and unbiased evaluation of treatment effectiveness.

Despite the increasing number of studies on Cinacalcet and SHPT, a comprehensive analysis of the existing literature using machine-learning techniques is lacking. Therefore, we conducted a review that included both bibliometric and meta-analyses to comprehensively analyze the literature on Cinacalcet and SHPT. The findings provide comprehensive information regarding the development, hotspots, and future directions within the research fields of Cinacalcet and SHPT. We believe that the insights gained from this study will be of interest to clinicians and researchers.

2 Methods

2.1 Source of data and searching strategy

Until November 2022, the Web of Science Core Collection database (WoSCC) was searched using the following searching strategy: TS=('secondary hyperparathyroidism' or 'SHPT') AND ('Cinacalcet' or 'Mimpara' or 'Sensipar' or 'AMG 074' or 'AMG 073' or 'KRN 1493' or 'Naphthalene') AND publishing year= (2000-2022). The raw data were retrieved from the Web of Science Core Collection (WoSCC). The rationale for choosing the WoSCC is that it is a cross-disciplinary data source that can provide more comprehensive information.

2.2 Procedure of bibliometric analysis

The inclusion criteria were as follows: (1) language: English; (2) period: 2000–2022; (3) literature type: articles and reviews. All included studies were exported from WoSCC. Each document record included the article title, keywords, author information, publication date, national sources, and other information. Figure 1 illustrates the literature screening process used in this study.

The "Bibliometrix" package in the R platform (Version 4.1.2; 23), VOSviewer (Version 1.6.18; 24), and CiteSpace (Version 5.8R3;

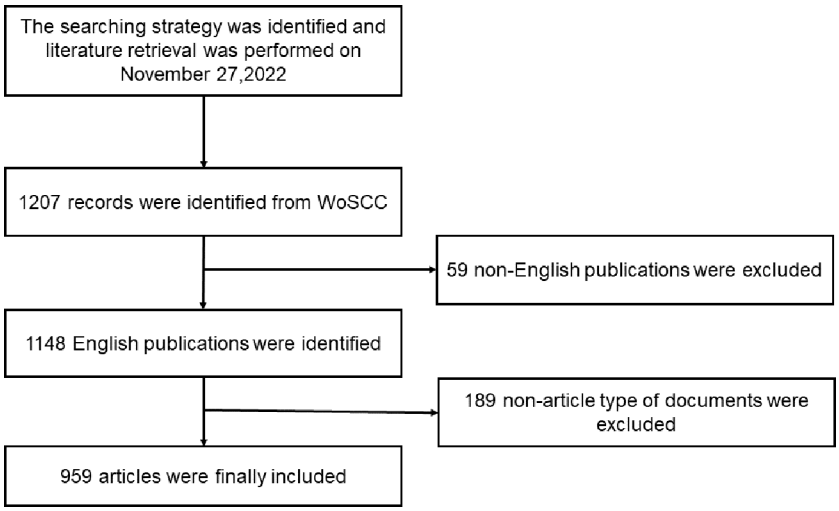

FIGURE 1
Flowchart of literature screening. WoSCC, Web of Science Core Collection.

25) were used for statistical and visual analysis of literature. Specifically, Bibliometrix was primarily used to analyze documents, count the number of publications and citations, and display cooperation among countries. CiteSpace was used to plot keyword timelines based on the frequency and time of keyword occurrence. VOSviewer was used for network analyses (e.g., collaborative analysis among authors).

We used the Python platform for the Latent Dirichlet Allocation (LDA) theme modeling (26). LDA determines the topic distribution based on the frequency with which vocabulary appears in documents (27). This method has been used in many research areas to identify research topics and trends in publications (e.g., 28, 29). The number of LDA topics was determined based on consistency. The number of topics with a consistency closer to 0.7 in the LDA topic model was considered the ideal (30). The LDA theme model can produce a frequency distribution of topics and theme words. Two of our researchers named each topic based on the distribution of theme words after discussion and analysis.

2.3 Procedures of meta-analysis

To be included in the meta-analysis, all articles had to meet the following criteria:1) they must be designed as randomized controlled trials (RCTs); 2) the interventions studied must include both cinacalcet and a control group, and 3) the articles must report clinical outcomes, including serum PTH, calcium, phosphate, and hypocalcemia.

Data extraction was performed independently by two researchers and any discrepancies were resolved through discussion with a third researcher. The recorded data included the author, year, country, intervention, number of participants, age, dosage strategy, the daily dose (minimum and maximum in mg), CKD stage, study duration, follow-up duration (in months), and clinical outcomes such as serum PTH (pg/ml), calcium (Ca; mg/dl), phosphate (P; mg/dl), calcium phosphate products, all-cause mortality, nausea, vomiting, cardiovascular mortality, hypocalcemia, and parathyroidectomy.

The quality of the RCTs was evaluated using the Cochrane Collaboration tool for assessing the risk of bias in randomized trials (31), which assessed the following aspects: random sequence generation, allocation concealment, blinding of patients and study personnel, blinding of outcome assessment, incompleteness of outcome data, selective reporting of outcomes, and other biases.

A meta-analysis was conducted using Review Manager software (version 5.0; The Cochrane Collaboration, Oxford, UK) and STATA software (version 11; Stata Corporation, College Station, TX, USA). For continuous variables (i.e., PTH, calcium, phosphate, and calcium phosphate products), we calculated the mean difference/standardized mean difference (*MD/SMD*) and 95% confidence intervals (95% *CI*). Nominal variables (all-cause mortality, nausea, vomiting, cardiovascular mortality, hypocalcemia, and parathyroidectomy) were analyzed using risk ratios (*RR*) and 95% CI. Heterogeneity was assessed using the I^2 statistic, with a random-effects model for I^2 greater than 50% and a fixed-effects model for I^2 less than 50%. Egger's test was used to examine publication bias, with statistical significance set at $p < 0.05$.

3 Results

3.1 Annual productions

A total of 959 articles, published between 2000 and 2022, were retrieved. The annual publication rate has shown a growing trend over the past 22 years (Figure 2). Only 56 articles were published prior to 2005. A sharp increase was observed in 2005 when the annual number of articles increased to 38. In 2008, this number peaked at 66. The number of outputs remained steady at approximately 50 articles per year.

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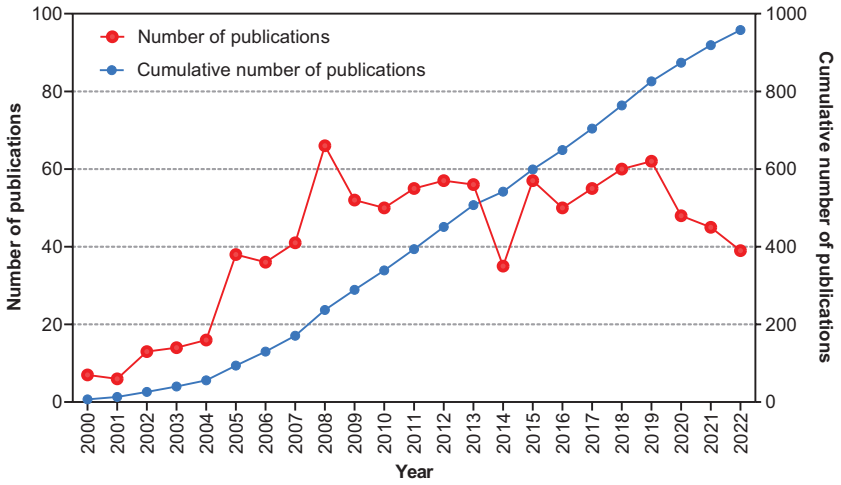

FIGURE 2
Number of publications and cumulative number of publications.

3.2 Countries

Researchers from 54 countries have contributed to this research area. The top ten productive countries were the U.S. (n = 267), Japan (n = 152), China (n = 65), Italy (n = 63), Spain (n = 63), France (n =44), Germany (n = 39), the United Kingdom (U.K., n = 28), Canada (n = 18), and Poland (n = 18; Table 1).

An international collaboration map was generated using the Bibliometrix R package (Figure 3; the line thickness indicates the frequency of collaboration among countries). As shown in the Figure, as the most productive country, the U.S. had already built the most international collaborations worldwide, while Japan (i.e., the second most productive country) had only collaborated with a few North American and European countries in this research field.

TABLE 1 The top-ten most productive countries over the period of 2000-2022.

Country	NP	SCP	MCP	MCP Ratio
U.S.	267	209	58	0.217
Japan	152	140	12	0.079
China	65	58	7	0.108
Italy	63	48	15	0.238
Spain	63	45	18	0.286
France	44	30	14	0.318
Germany	39	26	13	0.333
U.K.	28	19	9	0.321
Canada	18	6	12	0.667
Poland	18	17	1	0.056

NP, Number of publications; SCP, Number of single country publication; MCP, Number of multiple countries publication; MCP ratio, MCP as a proportion of total publications.

3.3 Institutions

A total of 1416 institutions were involved in Cinacalcet and SHPT research. The top-ten institutions were composed of four Japanese institutions, and four American institutions, while Italy and Spain each had one including Showa University (Japan, n = 89), Tokai University (Japan, n = 87), Kobe University (Japan, n = 50), University of California Los Angeles (UCLA, U.S., n = 47), Osaka City University (Japan, n = 44), University of Milan (Italy, n = 42), Stanford University (U.S., n = 40), Indiana University (U.S., n = 39), Hospital Clinic Barcelona (Spain, n = 36), and University of California San Francisco (U.S., n = 32). Figure 4 shows the institutional productivity over time. UCLA and Kobe University were the two of the earliest to publish studies in this area. Later, Showa University and Tokai University began to pay attention to this field and soon emerged as the most productive institutions.

3.4 Authors

A total of 3573 authors were involved in Cinacalcet and SHPT research over the years. The ten most productive authors are listed in Table 2. Dr. William Goodman from the University of California, Los Angeles (U.S.), had the highest h-index (i.e., An author-level citation metric that measures both the productivity and citation impact of publications; 32) and most citations followed by Dr. Misato Fukagawa (Tokai University, Japan) and Dr. Geoffrey Block (Denver Nephrology, U.S.), with h-indexes of 19 and 18, respectively. Figure 5 shows the collaborations among authors, which can be roughly classified into nine research groups.

3.5 Journals

In total, 940 articles were published in 320 journals. Table 3 displays the top ten journals that published the most articles

10.3389/fendo.2023.1146955

including *Nephrology Dialysis Transplantation* (*n* = 63), *Kidney International* (*n* = 37), *Therapeutic Apheresis and Dialysis* (*n* = 35), *Clinical Journal of the American Society of Nephrology* (*n* = 29), *Clinical Nephrology* (*n* = 25), *BMC Nephrology* (*n* = 20), *American Journal of Kidney Diseases* (*n* = 18), *Journal of the American Society of Nephrology* (*n* = 17), *Pediatric Nephrology* (*n* = 16), and *Plos One* (*n* = 16). *Nephrology Dialysis Transplantation* seems to be the most influential journal in the field with an h-index of 32 and 3098 total citations.

According to Bradford's law analysis, 13 journals were identified as core journals (Figure 6) including *Nephrology Dialysis Transplantation*, *Kidney International*, *Therapeutic Apheresis and Dialysis*, *Clinical Journal of the American Society of Nephrology*, *Clinical Nephrology*, *BMC Nephrology*, *American Journal of Kidney Diseases*, *Journal of the American Society of Nephrology*, *Pediatric Nephrology*, *Plos One*, *Transplanation Proceedings*, *Clinical and Experimental Nephrology*, and *Current Opinion in Nephrology and Hypertension*.

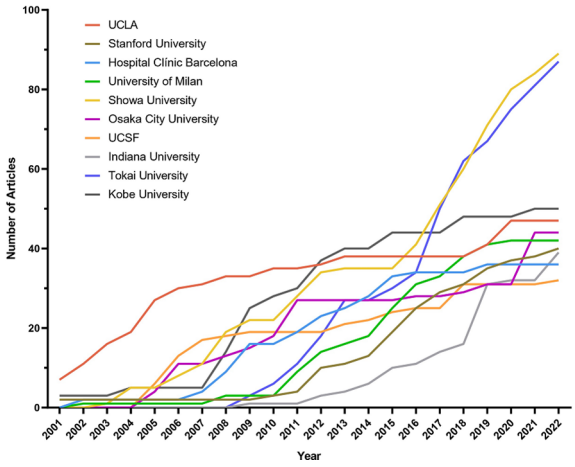

FIGURE 4
Productivity of the top-ten institutions over the period of 2000-2022. UCLA, University of California Los Angeles; UCSF, University of California San Francisco.

3.6 Articles

We used the R bibliometrix package to identify the top ten most-cited articles (Table 4). The most cited article was KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD, an updated guideline for the diagnosis and treatment of CKD-MBD. Of the ten articles, nine were RCTs on the effect of cinacalcet in the treatment of SHPT; the other was a guideline.

3.7 Topic modeling

Topic modeling can classify themes and discover hidden themes (33). We determined that the optimal number of topics for this study was three (Figure 7). By applying LDA-based topic analysis, we identified the three most popular topics within this research field (Table 5) including Topic 1, the comparative effects of various treatments: cinacalcet, telcalcetide, calcimimetic, parathyroidectomy, Vitamin D, Evocalcet; Topic 2, safety and efficacy: PTH level, serum

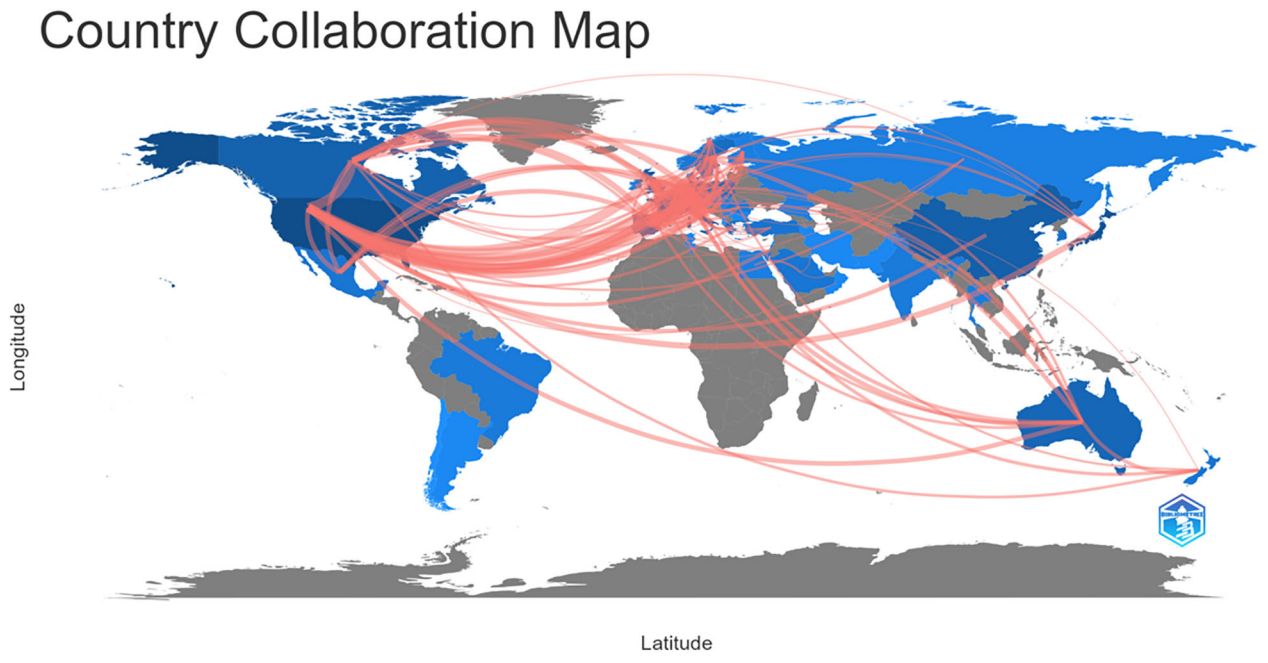

FIGURE 3
International collaboration map generated by Bibliometrix.

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TABLE 2 The top-ten most productive authors over the period of 2000-2022.

Author	H_Index	TC	NP	PY_Start
Fukagawa M.	19	1225	50	2008
Chertow G.M.	18	2796	33	2005
Goodman W.G.	21	2899	32	2000
Akizawa T.	12	525	31	2003
Block G.A.	18	2809	25	2003
Komaba H.	14	576	25	2008
Moe S.M.	13	2713	22	2003
Floege J.	13	1695	17	2010
Messa P.	10	549	17	2006
Martin K.J.	13	1697	15	2003

NP, number of publications; TC, Total citations; PY_Start, The year of their first publication in this field.

calcium, serum phosphate, vascular calcification, cardiovascular events, and mortality, and Topic 3, fibroblast growth factor-23 (FGF-23), paricalcitol, phosphate, and calcitriol. A time distribution analysis was then performed to detect the development of the top-ten keywords (Figure 8).

3.8 Citation burst

Burst keywords can be regarded as indicators of emerging trends (25). Burst detection analysis was conducted using CiteSpace software. Figure 9 shows the 18 keywords with the strongest citation bursts between 2012 and 2022 (red indicates the time at which a citation burst was identified). The most recent burst keywords were patients receiving hemodialysis, serum PTH, etelcalcetide, children, bone disorder, management, Vitamin D analog, and efficacy.

3.9 Meta-analysis

We conducted a meta-analysis of 24 RCTs with 9130 participants. The characteristics of the retrieved studies are presented in Table 6. A summary of the selection bias is presented in Supplementary 1, in which all included articles demonstrated high quality and low risk of bias. Egger's test was used to assess the possibility of publication bias. Funnel plot analysis did not reveal any significant publication bias (Supplementary 2).

The effects of Cinacalcet on serum indicators, including PTH, calcium, phosphate, and calcium-phosphate, were evaluated in this study (see Figure 10). Twenty-one studies comprising 3280 observations, were included in a pairwise meta-analysis to investigate the effects of Cinacalcet on serum PTH levels. The random-effects model revealed a statistically significant *SMD* of -0.56 (95% *CI* = -0.76, -0.37, z = -5.57, p = 0.001). Substantial heterogeneity was observed among the studies (I^2 = 82.0%, p =

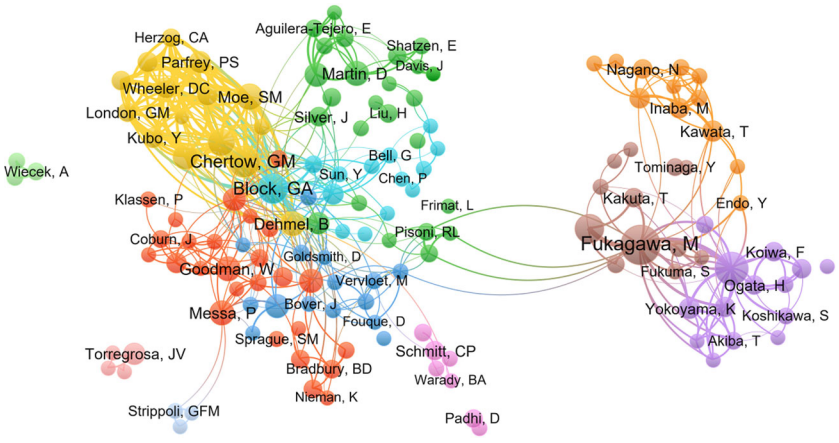

FIGURE 5
Co-authorship cluster map generated by VOSviewer.

TABLE 3 The top-ten journals published most articles regarding Cinacalcet and secondary hyperparathyroidism research.

Journal	H_Index	TC	NP	PY_Start
Nephrology Dialysis Transplantation	32	3098	63	2002
Kidney International	24	2584	37	2000
Therapeutic Apheresis and Dialysis	13	380	35	2005
Clinical Journal of The American Society of Nephrology	23	1839	29	2006
Clinical Nephrology	12	376	25	2005
BMC Nephrology	9	214	20	2012
American Journal of Kidney Diseases	12	607	18	2004
Journal of the American Society of Nephrology	15	1860	17	2000
Transplantation Proceedings	10	207	16	2006
Pediatric Nephrology	9	226	16	2003

TC, Total citations; NP, number of publications; PY_Start, The year of their first publication in this field.

0.001). The calcium analysis included 18 studies comprising 3282 observations. The random-effects model revealed a significantly negative *SMD* of -0.93 (95% *CI* = -1.21 to -0.64; z = -6.44, p = 0.001), indicating a moderate effect size in favor of the intervention. Heterogeneity was high (I^2 = 84.5%, p < 0.01). Based on the analysis of phosphate, the random effects model found a significant overall effect size of -0.17 (95% *CI* = -0.33 to -0.01, z = -2.13, p = 0.033). Heterogeneity analysis revealed a moderate-to-high level of heterogeneity among the studies (I^2 = 70.0%, p < 0.01), indicating a substantial variation in effect sizes across studies. Ten studies were included in the analysis of serum calcium-phosphate product levels, comprising 2388 observations. The random-effects model showed a significant overall effect of the intervention (*SMD* = -0.49, 95% *CI* = -0.71, -0.28, z = -4.55, p = 0.001), indicating a moderately beneficial effect. However, there was significant heterogeneity among the studies (I^2 = 79.1%, p = 0.001), indicating that the effect size estimates varied considerably.

We investigated the relationship between Cinacalcet and adverse events, including all-cause mortality, cardiovascular mortality, and parathyroidectomy (Figure 11). In terms of the relationship between Cinacalcet and all-cause mortality (n = 7586), our random effects model yielded a pooled *RR* of 0.97, 95% *CI* = 0.90 to 1.05], z = -0.73, p = 0.47. There was no significant difference in all-cause mortality observed in individuals taking Cinacalcet. Additionally, there was no evidence of heterogeneity across studies, with I^2 = 0.0%, p = 0.95. Our analysis of the association between Cinacalcet use and cardiovascular mortality showed no significant differences between groups. The pooled *RR* estimate was 0.69 (95% *CI*:0.36 to 1.31, p = 0.25). The test for heterogeneity was not statistically significant (I^2 = 0.0%, p = 0.612),

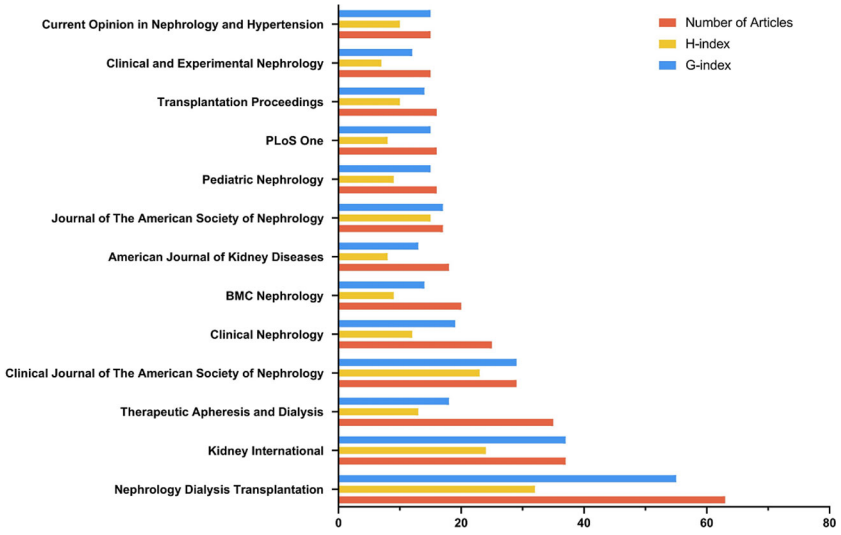

FIGURE 6
The core journals identified by Bradford's law. (Bradford's Law describes the logarithmic distribution of articles across a limited number of core journals in a subject area).

TABLE 4 The top-ten most cited articles about Cinacalcet and secondary hyperparathyroidism over the period of 2000-2022.

Article	DOI	Normalized TC
KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of CKD-MBD	10.1016/j.kisu.2017.04.001	28.26
Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis	10.1056/NEJMoa031633	11.11
Effect of Cinacalcet on cardiovascular disease in patients undergoing dialysis	10.1056/NEJMoa1205624	18.80
The ADVANCE study: A randomized study to evaluate the effects of Cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis	10.1093/ndt/gfq725	16.96
Effects of the calcimimetic Cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism	10.1111/j.1523-1755.2005.00596.x	4.64
Cinacalcet HCl, an oral calcimimetic agent for the treatment of secondary hyperparathyroidism in hemodialysis and peritoneal dialysis: A randomized, double-blind, multicenter study	10.1681/ASN.2004060512	4.07
Achieving NKF-K/DOQI bone metabolism and disease treatment goals with Cinacalcet HCl	10.1111/j.1523-1755.2005.67139.x	3.05
The Calcimimetic agent AMG 073 lowers plasma parathyroid hormone levels in hemodialysis patients with secondary hyperparathyroidism	10.1681/ASN.V1341017	4.62
Cinacalcet, fibroblast growth factor-23, and cardiovascular disease in hemodialysis: The EVOLVE Trial	10.1161/CIRCULATIONAHA.114.013876	7.49
The calcium-sensing receptor in normal physiology and pathophysiology: a review	10.1080/10408360590886606	2.62

TC, Total citations; KDIGO, The kidney disease: improving global outcomes; CKD-MBD, Chronic kidney disease - mineral and bone disorder; ADVANCE, Assessing donor variability and new concepts in eligibility; HCl, Cinacalcet hydrochloride; EVOLVE, Evaluation of Cinacalcet HCl therapy to lower cardiovascular events.

suggesting a low heterogeneity among the studies. Six studies with a total of 4901 participants were included to investigate the association between cinacalcet and parathyroidectomy. The random effects model showed a pooled *RR* of 0.36, 95% *CI* = 0.09 to 1.35, z = -1.51, p = 0.13, indicating no significant difference in parathyroidectomy between groups. The test for heterogeneity showed moderate heterogeneity between the studies, with an I^2 value of 72.6%, $p < 0.01$.

The safety of Cinacalcet was evaluated in this meta-analysis (Figure 12) by examining its association with nausea, vomiting, and hypocalcemia. The analysis of nausea included 19 studies with 8,127 observations. The results showed a random effects model *RR* of 2.29 (95% *CI* of 1.73 to 3.05, p = 0.001), indicating a statistically significant association between Cinacalcet use and nausea. The heterogeneity test revealed significant heterogeneity (I^2 = 46.4%, p = 0.01). The analysis of vomiting included 16 studies with 7,986

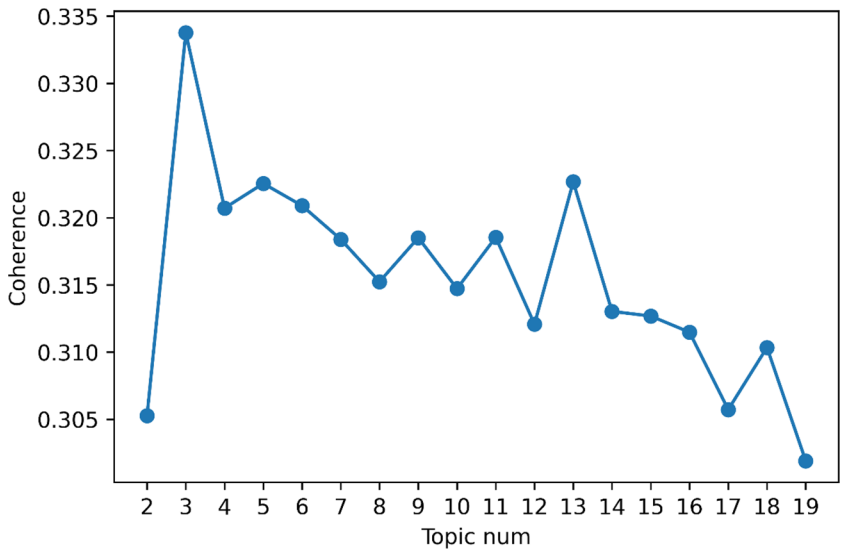

FIGURE 7
Number of topics-coherence score graph.

TABLE 5 Research topics generated by Latent Dirichlet Allocation analysis.

Topic		Keywords
1	Comparative effectiveness	Cinacalcet, Etelcalcetide, Evocalcet, Parathyroidectomy, Vitamin D, Therapy, Hemodialysis Patients, Kidney Disease, Secondary Hyperparathyroidism, Clinical Trial, Calcimimetic, PTH, Serum Calcium, Cardiovascular Events, Vascular Calcification, Complication, Nausea, Vomit, Hypocalcemia, Mortality
2	Safety and efficacy	Cinacalcet, Secondary Hyperparathyroidism, Therapy, Calcimimetic, Hemodialysis, Calcium, Phosphate, PTH, Parathyroidectomy, Management, Kidney Disease, Complication, Hypocalcemia, Mortality, Calcification, Hyperplasia, Parathyroid, Alkaline Phosphatase, Calcium-Sensing Receptor, Trial
3	FGF-23	PTH, Kidney Disease, Therapy, Secondary Hyperparathyroidism, FGF-23, Cinacalcet, Hemodialysis, Vitamin D, Calcium, Phosphate, Mortality, Bone Disease, Marker, Management, CKD-MBD, Kidney, Skeletal, Complication, Cardiovascular Events, End-Stage Renal Disease

FGF-23, fibroblast growth factor-23; PTH, parathyroid hormone; CKD-MBD, Chronic kidney disease - mineral and bone disorder.

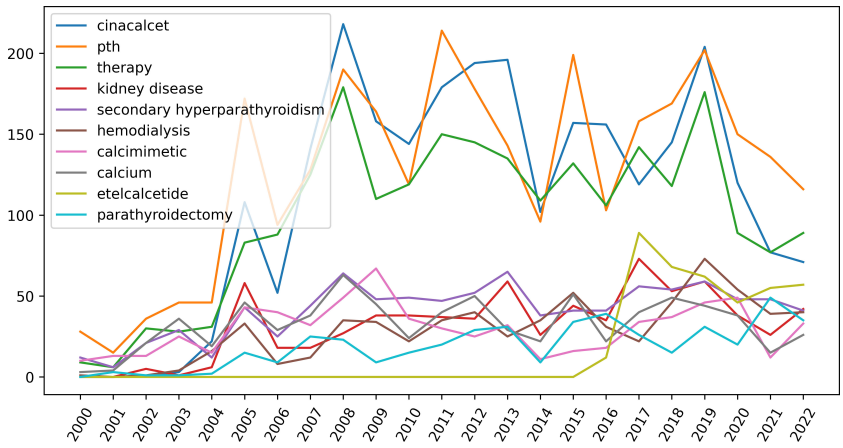

FIGURE 8
The development of the top-ten keywords generated by Latent Dirichlet Allocation (LDA) analysis. (LDA is a topic modeling method being used to determine hidden themes from large texts).

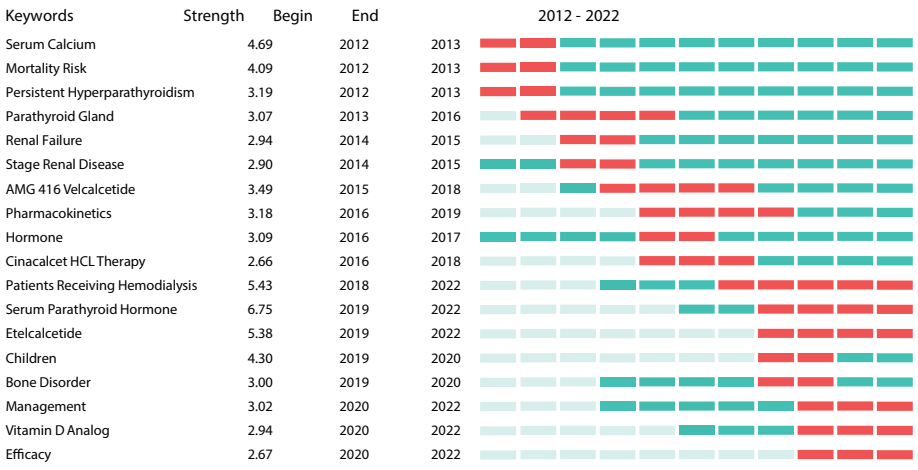

FIGURE 9
Strongest citation burst generated by CiteSpace.

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TABLE 6 Characteristics of meta-analysis included studies.

Author	Year	Country	Stage of CKD	Arm1	Arm2	Age1	Age2	Duration of the trial	Outcome	Follow up
Akiba	2008	Japan	HD	Cinacalcet, 12.5、25、50 mg/d,N=90	Placebo, N = 30	N	51.8 ± 7.5	3 weeks	Serum PTH, Ca,P, calcium-phosphate product,nausea, vomiting, hypocalcemia and Cardiac disorders	2 weeks
Goodman	2000	USA	HD	R-568, 100 mg/d,N=16	Placebo, N = 5	48.6 ± 12.4	54.7 ± 16.8	15 days	Serum PTH, nausea and hypocalcemia	0.5 months
Goodman	2002	USA	HD	AMG 073, 10–50 mg/d, N=23	Placebo, N = 7	N	N	8 days	Serum PTH, Ca and P	0.25 months
Lindberg	2003	USA	HD	AMG 073, 10–50 mg/d, N=38	Placebo, N = 39	52.7 ± 16.4	48.8 ± 15.6	4.5 months	All-cause mortality, pth, Ca, P,nausea and vomiting	4.5 months
Quarles	2003	USA	HD	AMG 073, 25–100 mg/d, N=36	Placebo, N = 35	49.6 ± 8.5	47.9 ± 14.2	18 weeks	Serum PTH, Ca,P, calcium- phosphate product	4.5 months
Block	2004	USA	HD	Cinacalcet, 30–180 mg/d,N = 371	Placebo, N = 370	54 ± 14	55 ± 15	26 weeks	Serum PTH, Ca,P, calcium- phosphate product,nausea, vomiting, hypocalcemia, hypotension and all-cause mortality	6.5 months
Charytan	2005	USA	CKD,not receiving dialysis	Cinacalcet, 30–180 mg/d, N = 27	Placebo, N = 27	60.6 ± 15.6	61.9 ± 15.1	18 weeks	Serum PTH, nausea, Cardiovascular mortality and all-cause mortality	4.5 months
Lindberg	2005	USA	HD PD	Cinacalcet, 30–180 mg/d,N = 371	Placebo, N = 101	51.8 ± 14	53.5 ± 13.9	26 weeks	Serum PTH, calcium, phosphate, calcium phosphate product, all-cause mortality, nausea, and vomiting.	6.5 months
Fishbane	2008	USA	HD	Cinacalcet,30–180 mg/d plus paricalcitol 2 g or doxercalciferol 1 g,N =87	Paricalcitol 2 g or doxercalciferol 1 g, N=86	57.7 ± 14.9	59 ± 12.4	27 weeks	All-cause mortality, nausea, vomiting, hypercalcemia, and hypocalcemia.	6.75 months
Fukagawa	2008	Japan	HD	Cinacalcet, 30–180 mg/d;N = 72	Placebo, N = 71	54.7 ± 11	55.7 ± 11.7	14 weeks	Serum calcium, phosphate, calcium phosphate product, nausea, vomiting, and hypocalcemia	3.5 months
Messa	2008	Italy	HD	Cinacalcet, 30–180 mg/d,N = 368	Conventional Care,N = 184	58.5 ± 14.5	58.3 ± 14.5	23 weeks	Serum PTH, calcium, phosphate, calcium phosphate product, all-cause mortality, cardiovascular mortality, nausea, vomiting, and hypocalcemia.	0.25 months
Chonchol	2009	USA	CKD,not receiving dialysis	Cinacalcet, 30–180 mg/d, N = 302	Placebo,N = 102	64.7 ± 13.3	66.2 ± 12.2	32 weeks	Serum calcium, phosphate, calcium phosphate product, all-cause mortality,	8 months

(Continued)

10.3389/fendo.2023.1146955

TABLE 6 Continued

Author	Year	Country	Stage of CKD	Arm1	Arm2	Age1	Age2	Duration of the trial	Outcome	Follow up
									cardiovascular mortality, nausea, vomiting, and hypocalcemia.	
EI-Shafey	2011	Egypt	HD	Cinacalcet, 30–180 mg/d,N = 55	conventional therapy, (intravenous alfacalcidol thrice weekly at the end of their dialysis session and phosphate binders), N = 27	51.5 ± 12.7	51.8 ± 15	36 weeks	Serum PTH, calcium, phosphate, calcium phosphate product, all-cause mortality, nausea, vomiting, and hypocalcemia.	9 months
Raggi	2011	USA	HD	Cinacalcet, 30–180 mg/d plus low-dose vitamin D,N = 180	Same dose of vitamin D prescribed N = 180	61.2 ± 12.6	61.8 ± 12.8	52 weeks	All-cause mortality and hypocalcemia.	12 months
Chertow	2012	USA	HD	Cinacalcet, 30–180 mg/d,N = 1948	Placebo, N = 1935	55.0 (35–74)	54.0 (35–73)	20 weeks	All-cause mortality, cardiovascular mortality, nausea, vomiting and hypocalcemia.	64 months
Ketteler - intra venous stratum	2012	Germany	HD	Cinacalcet (dose unclear) plus low-dose vitamin D,N = 64	Paricalcitol 0.07 μg/kg IV or iPTH/60 PON = 62	59.9 ± 12	61.2 ± 12.7	28 weeks	All-cause mortality, cardiovascular mortality, nausea, vomiting, hypercalcemia, and hypocalcemia.	7 months
Ketteler- 2-oral stratum	2012	Germany	HD	Cinacalcet (dose unclear) plus low-dose vitamin D,N = 70	Paricalcitol 0.07 μg/kg IV or iPTH/60 PON = 72	65.1 ± 12.5	65.7 ± 13.5	28 weeks	All-cause mortality, cardiovascular mortality, nausea, vomiting and hypocalcemia.	7 months
Kim	2013	Korea	HD	Cinacalcet, 25–50 mg/d plus low-dose vitamin D,N =33	Same dose of vitamin D prescribed N = 33	48.8 ± 11.5	47.2 ± 8.4	20 weeks	Serum PTH, nausea and hypocalcemia.	4 months
Urena-Torres	2013	USA	HD	Cinacalcet, 25–50 mg/d plus low-dose vitamin D,N =154	Same dose of vitamin D prescribed N = 155	57.9 ± 13.6	57.0 ± 14.6	52 weeks	All-cause mortality, nausea, vomiting and hypocalcemia.	12 months
Wetmore	2015	USA	HD	Cinacalcet, 30–180 mg/d,N = 155	vitamin D (dose unclear),N = 157	53 (21–81)	55 (22–86)	52 weeks	Serum PTH, calcium, phosphate, all-cause mortality and hypocalcemia.	24 months
Mei	2016	China	HD	Cinacalcet, 25–100 mg/d,N = 118	Placebo, N = 114	50.02 ± 11.17	50.12 ± 11.34	16 weeks	Serum PTH, calcium, phosphate, calcium phosphate product, nausea, vomiting, and hypocalcemia.	3.4 months
Akizawa	2018	Japan	HD	Cinacalcet, 25 mg/d,N = 30	Placebo, N = 30	58.1 ± 10.2	58.2 ± 10.4	30 weeks	cardiovascular mortality,nausea and hypocalcemia	0.75 months

(Continued)

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TABLE 6 Continued

Author	Year	Country	Stage of CKD	Arm1	Arm2	Age1	Age2	Duration of the trial	Outcome	Follow up
Fugakawa	2018	Japan	HD	Cinacalcet, 25-100 mg/d,N = 317	Evocalcet, 1-8 mg/d,N = 317	61.2 ± 11	61.5 ± 11.3	30 weeks	nausea, vomiting and hypocalcemia.	7.3 months
Susantitaphong	2019	Thailand	HD	Cinacalcet, 25-100 mg/d,N = 15	Placebo, N = 15	49.5 ± 11.9	49.4 ± 10.2	12 weeks	Serum PTH, calcium and phosphate	2.7 months
Eddington	2021	England	HD	Cinacalcet, 30-180 mg/d,N = 15	Placebo, N = 21	45 ± 16	54 ± 13	12 weeks	Serum PTH, calcium, phosphate, all-cause mortality and hypocalcemia.	12 months

CKD, Chronic kidney disease; HD, hemodialysis.

observations, and the random-effects model produced a pooled *RR* of 1.90 (95% *CI* = 1.70, 2.11, p = 0.001). The heterogeneity test revealed no significant heterogeneity (I^2 = 0%; p = 0.82). Finally, the analysis of hypocalcemia included 21 studies with 8,376 observations, and the random effects model produced a pooled *RR* of 4.05 (95% *CI* = 2.33 to 7.04, p = 0.001). The heterogeneity test revealed significant heterogeneity (I^2 = 79%, p < 0.01).

4 Discussion

We conducted a systematic review, including bibliometric and meta-analyses, to comprehensively analyze the literature on Cinacalcet and SHPT. This bibliometric review mapped the trends and patterns of Cinacalcet and SHPT publications by applying machine learning methods, further enriching previous reviews. This study captured the growth of these publications and the characteristics of the literature distribution, suggesting the critical role of Cinacalcet in SHPT research. Moreover, we applied advanced topic and keyword modeling methods to thoroughly understand the content of publications and explore the development of research topics and emerging trends. By applying LDA-based topic modeling analysis, three topics were generated including comparative effectiveness, drug safety assessment, and FGF-23.

Topic 1 mainly covered comparisons between Cinacalcet and other treatments. Parathyroidectomy, oral medications (e.g., Evocalcet and Cinacalcet), and intravenous medications (e.g., Etelcacetide and Upasita) are the three major treatment strategies for SHPT. Parathyroidectomy is the conventional treatment for SHPT. Compared to drugs, parathyroidectomy is better at reducing the level of serum calcium (14). However, parathyroidectomy may lead to low calcium levels, and there is also a risk of recurrence; therefore, surgery is typically not the first option (9). The

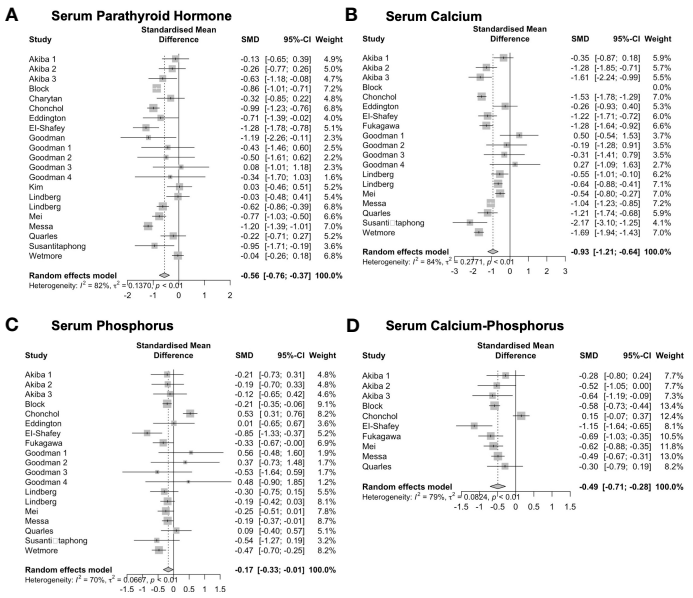

FIGURE 10
Forest plots demonstrating the effects of Cinacalcet on **(A)** serum parathyroid hormone, **(B)** calcium, **(C)** phosphate, and **(D)** calcium- phosphate.

10.3389/fendo.2023.1146955

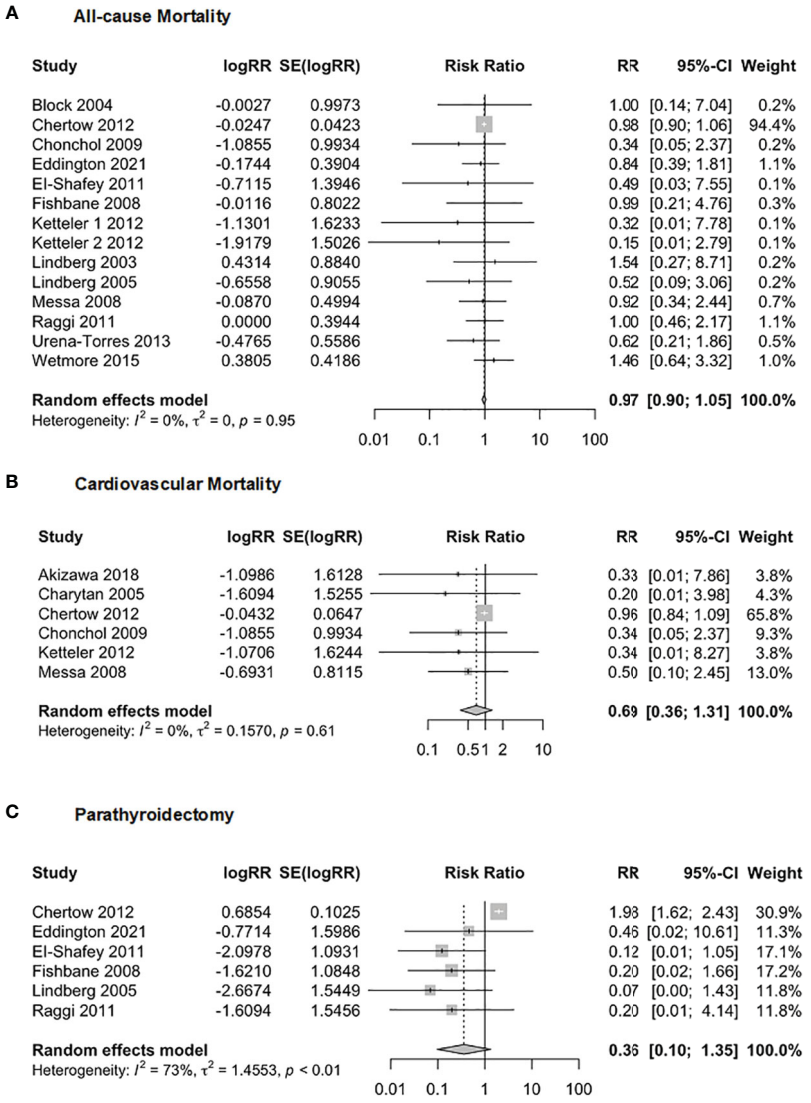

FIGURE 11
Forest plot demonstrating the association between Cinacalcet and risk for **(A)** allcause mortality, **(B)** cardiovascular mortality, and **(C)** parathyroidectomy.

availability of Cinacalcet has reduced the need for parathyroidectomy; however, surgery remains irreplaceable in patients with severe SHPT or who are drug-resistant (14). As the first FDA-approved calcimimetic medication, Cinacalcet is safe and effective. The major limitation of Cinacalcet is its gastrointestinal side effects, with approximately 15–30% of users reporting symptoms of nausea and/or vomiting (13). This is largely due to oral administration; therefore, the newly released calcimimetics, Etelcalcetide and Upasita, are both intravenously administered (34, 35). The comparison of Cinacalcet with other treatments is a research hotspot in this field. Through topic modeling analysis, we also noticed that combined therapies are increasingly being focused on. In recent years, researchers have conducted multiple trials to compare the efficacy of Cinacalcet plus supplements (e.g., Vitamin D and Calcitriol) versus Cinacalcet alone in the treatment of SHPT in recent years (36–38).

Topic 2 was generally safety and efficacy. PTH is a peptide hormone secreted by the parathyroid glands that controls the levels of serum calcium, phosphate, and vitamin D (6). Phosphate and calcium imbalances result in the secretion of excessive amounts of PTH, which is the primary pathological manifestation of SHPT (39). Elevated PTH levels are strongly associated with higher mortality and cardiovascular events in patients with CKD (39). The effectiveness of Cinacalcet in reducing PTH levels, thereby lowering the risk of death and cardiovascular events, has been confirmed by some researchers (11, 40). However, in some studies, Cinacalcet has not demonstrated superior efficacy compared with conventional treatments (41). The role of Cinacalcet in reducing adverse events remains inconclusive and has always been an important focus in this field. Researchers have also suggested that these effects may be moderated by the patient's age (17). In their study, Cinacalcet effectively decreased the risk of adverse events in older patients but not the younger individuals (17). This finding suggests that more demographic factors should be examined in future studies. Moreover, the European Medicines Agency recently approved the use of Cinacalcet in children aged > 3 years on dialysis

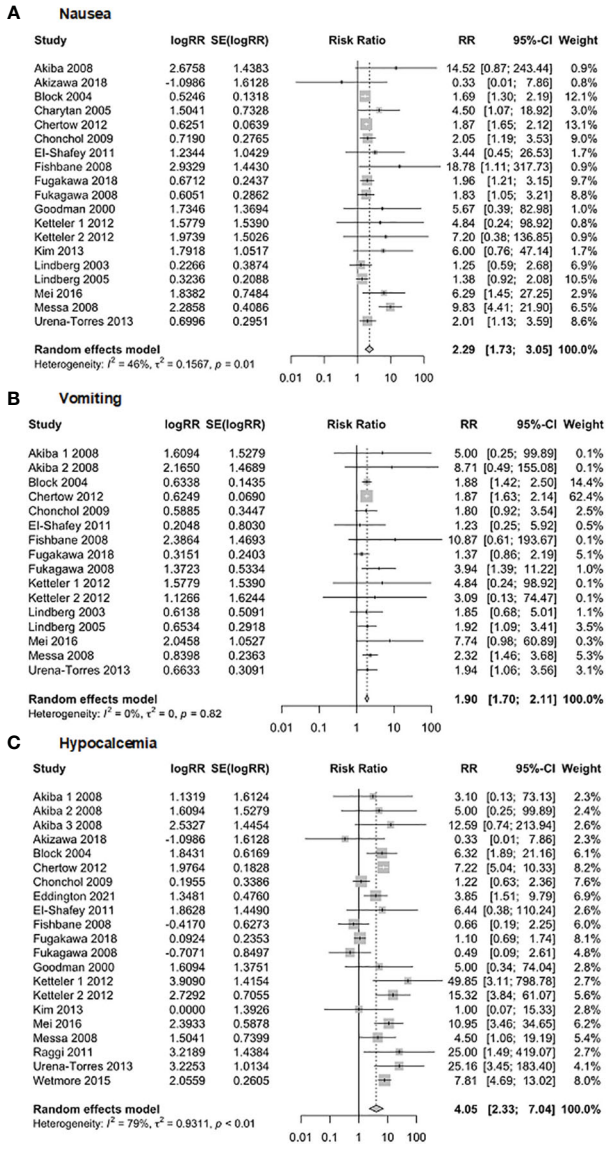

FIGURE 12
Forest plot demonstrating the safety of Cinacalcet: **(A)** nausea, **(B)** vomiting, and **(C)** hypocalcemia.

(until then, Cinacalcet was used only for adults; 42). Given the requirements of growth and development, many more factors need to be monitored and managed in pediatric SHPT (42). Although no approval for its use has been found in any region other than Europe, according to existing literature, Cinacalcet for pediatric use has attracted the attention of practitioners worldwide. The keyword citation burst results support this view.

Topic 3 was mostly related to FGF-23, which is an emerging hotspot. FGF-23 plays a central role bone-kidney-parathyroid axis and is associated with mortality and cardiovascular events in CKD (43, 44). FGF-23 is a bone-derived hormone that suppresses phosphate reabsorption and Vitamin D hormone synthesis in the kidney, and the resulting Vitamin D deficiency reduces calcium absorption and CaSR-mediated PTH inhibition (45, 46). FGF-23 is therefore regarded as a risk factor of CKD (47). Cinacalcet is effective in controlling PTH levels by inhibiting FGF-23 secretion and thus may play a role in decreasing the incidence of adverse events (48, 49). Moreover, in patients with end-stage renal disease, controlling FGF-23 has recently been found to be more effective in reducing cardiovascular events than controlling PTH (50, 51). FGF-23 is considered a new therapeutic target and is expected to be a promising field of investigation in the future (52).

Based on these findings, we conducted a meta-analysis to examine the clinical efficacy, adverse events, and safety of Cinacalcet. The results of this meta-analysis confirm the effects of Cinacalcet in patients with SHPT. Specifically, Cinacalcet use was associated with significant reductions in serum PTH, calcium, phosphate, and calcium-phosphate levels, indicating its beneficial effects on bone and mineral metabolism. However, significant heterogeneity was observed among the studies, suggesting that the effect of cinacalcet on these indicators may vary depending on patient characteristics, treatment protocols, and other factors. In terms of safety, the analysis found that Cinacalcet is associated with an increased risk of nausea, vomiting, and hypocalcemia. Although these adverse effects are generally mild to moderate in severity, they may limit the clinical utility of Cinacalcet in some patient populations. However, the overall incidence of adverse events associated with Cinacalcet is relatively low, suggesting that the benefits of the drug may outweigh its risks for many patients.

This study has a few limitations. First, only the WoSCC database was searched, which may have led to bias. Detailed and comprehensive knowledge can be obtained if other databases (e.g., Scopus and PubMed) are explored. Second, limited by the length of the journal manuscript, we cannot present all the results of our analyses (e.g., all the countries, authors, keywords, and citations). However, some information may have been missing from our study. Third, the meta-analysis included studies with significant variability in terms of patient populations, treatment protocols, and outcome measures, thus likely limiting the generalizability of these findings. Finally, although quantitative metrics reflect the popularity of scientific research, the results should be interpreted carefully.

5 Conclusions

For the first time, this systematic review included both bibliometric and meta-analytical methods that analyzed current publications on Cinacalcet and SHPT through machine learning, which is expected to be helpful for researchers in extracting objective and comprehensive clues from large amounts of data. Researchers from the U.S. and Japan started the earliest and made the greatest contributions to this field. The comparative effects of various treatments, safety and efficacy, and FGF-23 are the three major topics in this research field. Integrated treatment, Cinacalcet use in pediatric CKD, and new therapeutic targets are novel topics that have received increasing attention from researchers and clinicians. Through a meta-analysis, we confirmed that Cinacalcet was effective in reducing serum PTH and calcium levels and improving serum phosphate and calcium- phosphate levels; however, there was no difference in all-cause mortality,

cardiovascular mortality, and parathyroidectomy between Cinacalcet and non-Cinacalcet users. Moreover, Cinacalcet is associated with an increased risk of nausea, hypocalcemia, and vomiting. These findings have important implications for the management of patients with SHPT and highlight the potential benefits and risks of cinacalcet.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

Two authors, XL and WD, designed this study and collected and processed relevant data. The manuscript was written by XL and HZ. All authors have contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1146955/full#supplementary-material

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Parathyroid adenoma with rare severe pathological osteolytic lesion: a case report and literature review

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Parathyroid adenomas are benign proliferative disorders of parathyroid glands. Patients typically exhibit hyperparathyroidism and elevated serum calcium levels due to elevated levels of parathyroid hormone (PTH). We report a newly diagnosed case of a rare pathological osteolytic lesion. Radiological evaluation revealed multiple bony lesions in multiple parts of the pelvis, vertebral body, and spinous process, suggesting hematological neoplasms or bone marrow metastatic carcinoma. The morphology revealed many abnormal cells in the bone marrow smear. Furthermore, serum calcium and PTH levels were significantly increased compared to normal levels. Doppler color ultrasound showed a thyroid mass (left), suspected parathyroid adenoma, thyroid, and isthmus nodular goiter (right). The patient underwent bilateral neck exploration with parathyroidectomy, and serum calcium and PTH levels significantly decreased on the second day after surgery and had a surgical cure.

KEYWORDS

parathyroid adenoma, parathyroid hormone, serum calcium, pathological osteolytic lesions, parathyroidectomy

Introduction

Parathyroid adenoma is a type of parathyroid proliferative disease, including parathyroid hyperplasia, parathyroid adenoma, and parathyroid cancer. Eighty to 85% of patients with parathyroid adenomas typically exhibit hyperparathyroidism (1). Hyperparathyroidism has the potential to be aggressive and destructive (2). Bone involvement in hyperparathyroidism can manifest as subperiosteal resorption, systemic demineralization, or focal lytic lesions (3). However, only a few patients experience severe pathological osteolytic lesions. Herein, we report a unique case of pathological osteolytic lesions and the pretreatment diagnostic challenges faced in the differential diagnosis of a potential hematological neoplasm or bone marrow metastatic carcinoma.

Case report

A 42-year-old woman complained of general weakness for one week and had a history of fracture. Physical examination revealed no other special findings, except for bone pain. Complete Blood Count displayed small cell hypopigmentation anemia, and serum iron 3.60 μmol/L (normal, 9–27 μmol/L), unsaturated iron binding force 65.63 μmol/L (normal, 25–52 μmol/L). Accordingly, this patient was supposed to be diagnosed as iron deficiency anemia (IDA). However, computed tomography (CT) showed multiple low-density shadows in the L3 vertebral body, sacrum, pubis, ischium, and both femurs. Positron emission tomography-computed tomography (PET-CT) also showed elevated metabolism in the pelvis, suspected hematological neoplasms, and bone marrow metastatic carcinoma (Figure 1A). Immunofixation electrophoresis (IgG, IgA, IgM, κ, and λ) was negative. Many abnormal cells that were difficult to distinguish from multiple myeloma and metastatic carcinoma were found in the bone marrow smear (Figure 1B). Doppler color ultrasound showed a thyroid mass (left, 4.1 × 2.6 cm) (Figure 2A) and suspected parathyroid adenoma, thyroid, and isthmus nodular goiter (right, 0.4 × 0.2 cm) (Figure 2B). Blood biochemical index indicated serum calcium 3.38 mmol/L (normal, 2.11–2.52 mmol/L), serum phosphorus 0.77 mmol/L (normal, 0.82–1.62 mmol/L) and PTH 1,684 pg/L (normal, 15–65 pg/L). Therefore, parathyroid adenoma (left), thyroid, and isthmus (right) resections were performed under general anesthesia. Histopathological examination confirmed the diagnosis of parathyroid adenoma (Figure 1C). Pathologically, the left parathyroid gland area had 4 × 3.6 × 2.8 cm size nodular mass, section grayish-yellow, solid, soft, with an intact surface envelope. Right thyroid and isthmus with 5.7 × 5.5 × 1.1 cm size gray red tissue, a nodule with a diameter of 0.2 cm can be seen on the section at a distance of 0.2 cm from the capsule on the section, section gray white, solid, hard, with unclear boundaries. The patient recovered well postoperatively, serum calcium (2.67 mmol/L), serum phosphorus (0.64 mmol/L) and PTH (4.49 pg/L) also significantly decreased on second day after surgery (Figure 3).

Discussion

The parathyroid gland produces parathyroid hormone (PTH), which plays a key role in regulating the calcium balance in the body (4). Parathyroid adenoma is a type of parathyroid hyperplastic disease, which is characterized by primary hyperparathyroidism with elevated serum calcium and PTH levels. Patients with hyperparathyroidism present non-specific symptoms, such as fatigue, pain, and weakness (1).

This patient started with fatigue, and CT imaging showed low-density shadows of multiple parts of the body. MRI showed bone destruction of the L3 vertebral body and spinous process, and PET/CT fusion image showed bone destruction of the bilateral ilium with abnormal metabolism. Osteolytic lesions are common imaging changes in multiple myeloma and bone metastatic carcinomas (5, 6). However, the patient who underwent immunofixation electrophoresis yielded negative results. Many abnormal cells that were difficult to distinguish from osteoclasts were found in bone marrow smears. These cells were relatively large and different in size, and could be seen as polynuclear, the nuclei were mostly quasi-circular, the nuclear chromatin was relatively gathered, the cytoplasm was rich, dark blue, and the fusion between cells was observed, and hematological neoplasms or metastatic carcinoma were suspected.

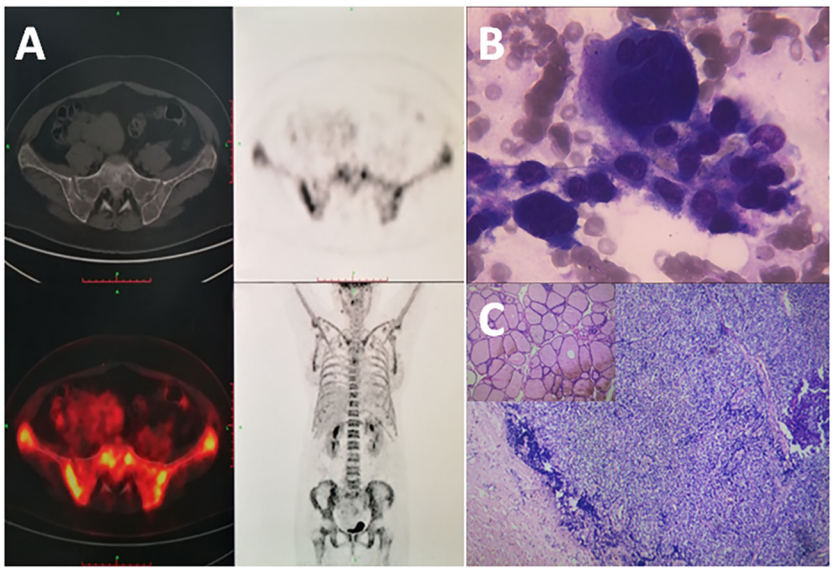

FIGURE 1
(A) Multiple low-density shadows and hypermetabolism in multiple parts of the pelvis with no significant imaging in the parathyroid gland on PET/CT examination. **(B)** Nuclear cells on bone marrow smear: Focal or fused distribution with deep staining of cytoplasm and nucleus (×1,000, Wright-Giemsa). **(C)** Thick collagen fiber capsule of the lesion (×100, hematoxylin–eosin), focal distribution of water-like transparent cells, with few stroma (×400, hematoxylin–eosin stain).

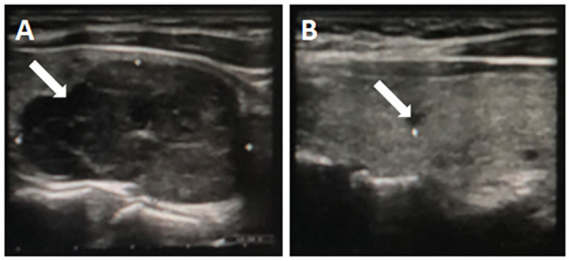

FIGURE 2
A large homogeneous mass (4.1 × 2.6 cm) with distinguishable boundaries in the lower pole of the left thyroid gland **(A)**, a hypoechoic nodule (0.4 × 0.2 cm) with unclear boundaries in the middle of the right thyroid gland **(B)**.

However, Doppler color ultrasound revealed a thyroid mass, thyroid, and isthmus nodular goiter, while serum calcium and PTH levels were significantly increased. Based on these results, the patient was clinically diagnosed with parathyroid adenoma. Therefore, the parathyroid adenoma, thyroid, and isthmus goiter were removed under general anesthesia. Based on the histopathology and clinical context, the tumor was identified as a parathyroid adenoma. The serum calcium and PTH levels also decreased significantly after parathyroidectomy.

Parathyroid adenoma is a benign tumor of the parathyroid gland that involves a single gland and is usually the main cause of primary hyperparathyroidism (80%), followed by parathyroid hyperplasia (15%), ectopic parathyroid adenoma (4%), and multiple parathyroid adenomas (1–2%) (7). In the differential diagnosis, it is necessary to distinguish it from multiple endocrine neoplasias because polyglandular and syndromic disorders associated with primary hyperparathyroidism are more likely (8). Nevertheless, this patient did not have any symptoms suggestive of syndromic involvement such as galactorrhea, headache, visual deficit, neuroglycemic symptoms, thyroid nodules or goiter, adrenergic phase, hypertension, or jaw tumor.

Parathyroid adenomas mainly occur in female aged 40–80 years (9, 10). Increased PTH serum levels are a common cause of hypercalciuria, which can manifest as recurrent kidney stones (11). However, in our patient, Doppler color ultrasound revealed no abnormalities or stones in the urinary system. Iwen et al. reported that the sestamibi scan has 68%–72% sensitivity and 99% specificity for detecting a parathyroid adenoma and can significantly improve the accuracy of diagnosis and the success of surgery (12). Thus, according to the meta-analysis, there were no significant differences between ultrasonography and parathyroid scintigraphy with 99mTc-MIBI in terms of sensitivity and specificity. There was overlap in the 99% confidence interval (13).

Currently, parathyroidectomy is the best choice for hyperparathyroidism to reduce the long-term destructive effect on bone and the negative effect of high serum calcium levels (14). Prevention of postoperative "hungry bone syndrome" is also important. The clinical symptoms caused by the rapid decline of high circulating levels of PTH after parathyroidectomy include bone deformation, fracture, and hypocalcemia (<2.1 mmol/L), which is called "Hungry Bone Syndrome" (15). Therefore, the patient was administered intravenous calcium repletion on the second postoperative day, followed by high-dose oral calcium and calcitriol supplementation and monitoring of serum calcium and PTH levels. At follow-up, the patient recovered well, and the serum calcium and PTH levels were within the normal range.

Conclusion

This is an extremely rare and easily misdiagnosed severe osteolytic lesion caused by parathyroid adenoma. This report contributes to improving the awareness of clinicians and pathologists that the clinical,

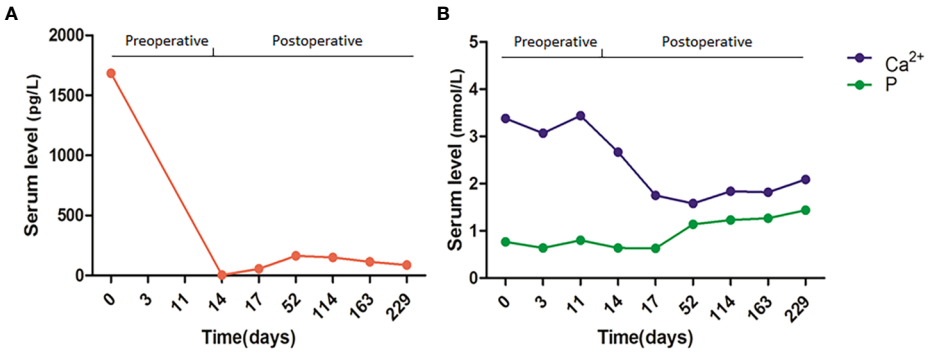

FIGURE 3
Dynamic monitoring of PTH **(A)** and serum calcium and phosphorus **(B)** levels preoperatively and postoperatively.

radiologic, and cytomorphological suspicion of hematological neoplasms or metastatic carcinoma may also be benign tumors. Clinicians and pathologists must keep in mind that parathyroid adenomas can cause osteolytic lesions and increase the number of osteoclasts, especially in hyperparathyroidism.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

JC collected clinical data. GT and YP diagnosed and followed up the patient. HC reviewed the literature and prepared the initial draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Ultrasound-guided microwave ablation in the treatment of recurrent primary hyperparathyroidism in a patient with MEN1: a case report

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Background: Multiple endocrine neoplasia type 1 (MEN1) is an inherited endocrine syndrome caused by the mutation in the tumor suppressor gene *MEN1*. The recurrence rate of primary hyperparathyroidism (PHPT) in patients with MEN1 after parathyroidectomy remains high, and the management of recurrent hyperparathyroidism is still challenging.

Case presentation: We reported a 44-year-old woman with MEN1 combined with PHPT who was diagnosed through genetic screening of the patient and her family members. After parathyroidectomy to remove one parathyroid gland, the patient suffered from persistent high levels of serum calcium and parathyroid hormone, which returned to normal at up to 8 months after ultrasound-guided microwave ablation (MWA) for bilateral parathyroid glands, suggesting an acceptable short-term prognosis.

Conclusion: Ultrasound-guided MWA for parathyroid nodules may be an effective therapeutic strategy for recurrent PHPT in MEN1 patients.

KEYWORDS

multiple endocrine neoplasia, primary hyperparathyroidism, microwave ablation, recurrence, case report

Abbreviations: MEN, Multiple endocrine neoplasia; PHPT, primary hyperparathyroidism; EA, ethanol ablation; RFA, radiofrequency ablation; LA, laser ablation; HIFU, high-intensity focused ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; PTH, parathyroid hormone; ECT, Emission computed tomography; ARR, plasma aldosterone/renin ratio; SPX, subtotal parathyroidectomy; TPX, total parathyroidectomy; LPX, less-than-subtotal parathyroidectomy; SGE, single gland resection; VRR, volume reduction rate.

Introduction

Multiple endocrine neoplasia (MEN) is a group of disorders characterized by adenomatous lesions in multiple endocrine glands. MEN patients develop tumors or hyperplasia successively in three endocrine glands and/or neuroendocrine tissues. MEN1 usually involves the pituitary, parathyroid, pancreas and other glands. Most of MEN1 patients suffer from primary hyperparathyroidism (PHPT) caused by parathyroid hyperplasia and/or adenoma (1). The incidence of involvement in two or more parathyroid glands by MEN1-related PHPT is remarkably higher than that of non-MEN-1-related PHPT (56% vs. 7%) (2). After surgery for parathyroid glands, MEN1-related PHPT persists or recurs in 14-69% of patients (3, 4), hypercalcemia in 50% at 8-12 years (5), and permanent hypoparathyroidism in 0-50% (3, 4).

Reoperation remarkably increases the incidence of complications in MEN1 patients with recurrent PHPT. Percutaneous ethanol ablation (EA) is a minimally invasive procedure characterized by lower risks of serious events than the conventional open surgery. EA has been implemented in MEN1 patients with recurrent PHPT (6, 7). PHPT and secondary hyperparathyroidism are treated with minimally invasive thermal ablation, including microwave ablation (MWA), radiofrequency ablation (RFA), laser ablation (LA) and high-intensity focused ultrasound (HIFU). However, its application to MEN1 patients combined with PHPT has not been reported. Recently, Han, et al. reported a 52-year-old MEN1 patient complicated with relapsed PHPT received ultrasound-guided RFA with a remarkable recovery (8). In the present study, we for the first time reported a case of MEN1 combined with relapsed PHPT who was successfully treated with ultrasound-guided MWA.

Case presentation

A 44-year-old woman presented for a pancreatic mass found during the physical examination. Abdominal computed tomography (CT) scan showed: (1) a lesion (38 mm×25 mm) occupying the tail of the pancreas (Figure 1A); (2) a lesion occupying the right adrenal gland and suspected as adenoma (Figure 1B); (3) small stones in the right kidney. Plain and contrast magnetic resonance imaging (MRI) scans of the pancreas showed: (1) a lesion occupying the tail of the pancreas and suspected as neuroendocrine tumor; (2) the right adrenal

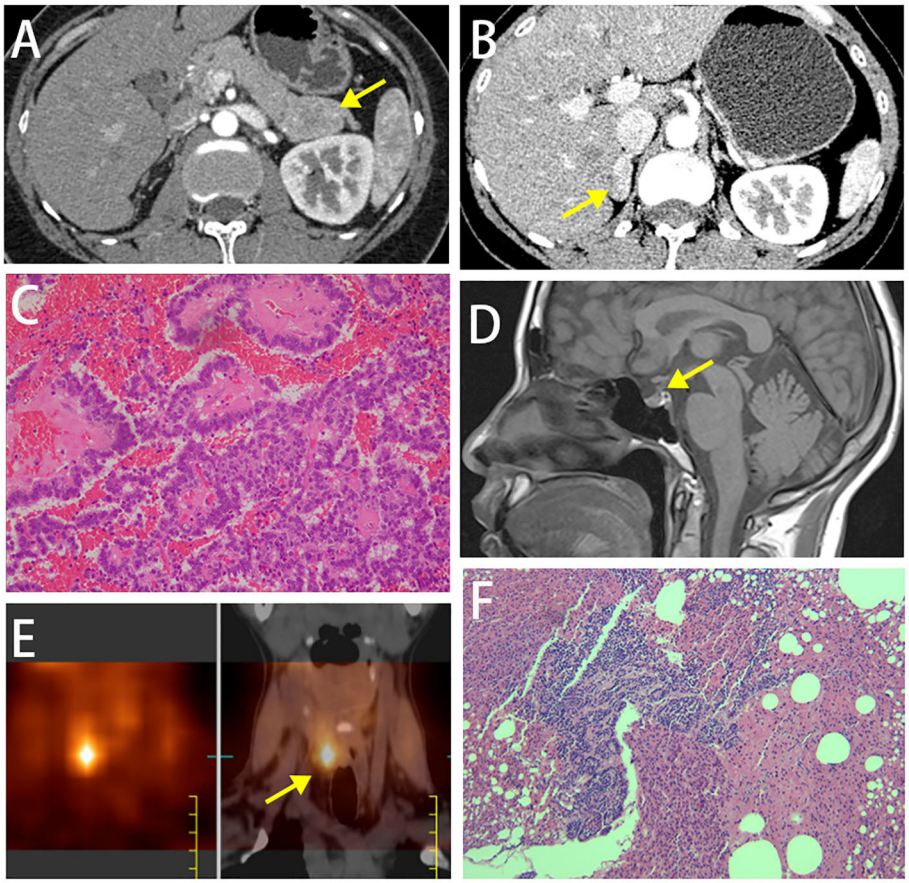

FIGURE 1
(A) Abdominal plain and contrast MRI scans of the pancreas showed a lesion occupying the tail of the pancreas. **(B)** Abdominal plain and contrast MRI scans of the pancreas showed a lesion occupying the right adrenal gland and suspected as adenoma. **(C)** Histopathological image of tissue pancreas tumor removed. **(D)** MRI scan of the pituitary gland. **(E)** Emission computed tomography (ECT) images on parathyroid glands showed one radioactive uptake. **(F)** Postoperative pathology showed nodular hyperplasia of the parathyroid gland.

adenoma (23 mm×12 mm). The patient received resection of pancreatic body and tail, and the postoperative pathology showed a soft, grayish-yellow mass (4 cm×3cm×2cm) with a clear margin in the tail of the pancreas. Tumor cells in the mass were uniform in size, mildly atypical, and arranged in papillary structure or solid sheets. No tumor cells were found in the resection margin of the tail of the pancreas. Immunohistochemistry results showed AE1/AE3 (+), CgA3 (+), Syn3 (+), Ki67 (about 4%), β-catenin in the membrane (+), α-ACT (+), progesterone receptor (PR, +), and Vimentin (-). G2 neuroendocrine tumor was finally diagnosed based on the pathological and immunohistochemical findings (Figure 1C). Serum calcium and parathyroid hormone (PTH) at postoperative 1 month were 2.65 mmol/L and 2847.6 pg/ml, respectively. The patient did not exhibit fatigue, nausea, vomiting, anorexia, abdominal pain, diarrhea, asthma, cough, lower limb pain, thirst, polyuria, constipation, hand and foot convulsions and mental changes during the course of disease.

Thyroid function tests at her age of 28 years were normal. Sex hormone binding globulin serum tests for measuring prolactin level at her age of 30 years were normal. The patient denied the history of medication. She had a healthy son. Her old brother had a medical history of hyperparathyroidism and kidney stones. Physical examinations of the patient showed slight thickening of bilateral toe joints.

Laboratory testing was performed. (1) blood routine tests: white blood cell count, 6.89×10^9/L; red blood cell count, 3.67×10^{12}/L; hemoglobin, 112 g/L; platelet count, 1.0×10^9/L; (2) biochemical tests: alanine aminotransferase, 40.4 U/L; aspartate aminotransferase, 56 U/L; albumin 36.9 g/L; creatine, 46 μmol/L; creatine clearance, 117.4 ml/min/1.73m^2; serum sodium, potassium, magnesium and phosphorus levels were normal; (3) urine specific proteins testing: urine α1-microglobulin<4 mg/L; urine IgG, 7.98 mg/L; urine transferrin <2 mg/L; Kappa and Lambda light chains of immunoglobulins in serum and urine were normal; Bence-Jones protein (-); 24-h calcium in urine, 5.55 mmol/L; (4) Multiple times of serum calcium and PTH testing showed abnormal increases (Supplementary Table 1).

An uneven signal intensity was detected on the plain MRI scan of the pituitary gland, and no abnormal findings were detected on contrast scans (Figure 1D). The dual-phase 99mTc-MIBI parathyroid scan revealed a soft-tissue-density nodule behind the inferior pole of the right thyroid lobe, considering a hyperfunctioning parathyroid mass (Figure 1E). Prolactin level of 59.2-120.55 ng/ml, as well as basal prolactin of 63.75 ng/ml and peak/baseline prolactin <1.5 detected by the metoclopramide test were suggestive of hyperprolactinemia. The elevated growth hormone (8.12-10.97 ng/ml↑) and 1-h glucose tolerance test of 8.05 ng/ml indicated the secretion of high-level growth hormone. The aldosterone blood test showed that the orthostatic plasma aldosterone/renin ratio (ARR) was 0.18; 24-h urine catecholamine, 24-hour urine cortisol and cortisol circadian rhythm were in the normal ranges, suggesting the nonfunctional adrenal adenoma. The gastrin level was 28.43 pg/ml↓. Painless gastrointestinal endoscopy showed chronic superficial gastritis with erosions and colonic diverticulum. A normal structure of the right accessory on the gynecological ultrasound scan excluded the possibility of ovarian tumors. A moderate-to-strong echo in the right kidney on the urinary system color Doppler ultrasound was suggestive of the hamartoma. Thyroid function tests and ultrasound did not suggest any thyroid disorder. Z-score of the bone mineral density of L1-4 was below -2.0. CT scan of the chest showed micronodules in both lungs. The patient was finally diagnosed as MEN1 by genetic testing (Supplementary Figure 1), revealing a novel mutation c.1520delG>T (p.G507Afs*52) in exon 10 of *MEN1* gene. Moreover, genetic testing was performed in the first-degree relatives of the patient, and the *MEN1* gene mutation was detected in the patient's father, old brother and nephew (Figure 2, Supplementary Figure 1).

The patient was treated with the surgical resection of the right inferior parathyroid gland in February 2022 in other hospital, and postoperative pathology showed nodular hyperplasia of the parathyroid gland (Figure 1F). Serum calcium and PTH were 2.9 mmol/L and 256.5 pg/ml right after surgery, and 2.78 mmol/L and 294.3 pg/ml at 3 months, respectively, suggesting that hyperparathyroidism was not completely relieved. ECT images on the parathyroid glands in June 2022 showed two adjacent radioiodine uptake tissues (hyperparathyroidism tissues) on the dorsal side of the right thyroid lobe, and one suspected radioiodine

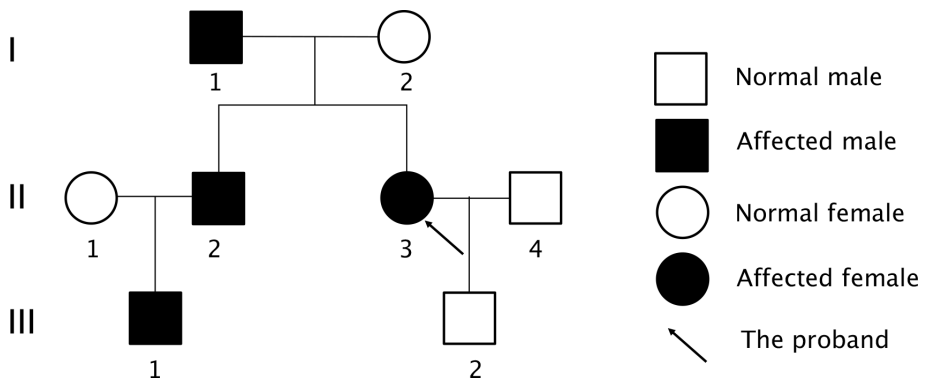

FIGURE 2
Pedigree diagram of the proband's family. Family members are indicated by generations (Roman numbers) and individuals (Arabic numbers). Circles indicated women and square indicated men. Clinical status was denoted: open symbols, normal; solid symbols affected.

uptake tissue on the dorsal side of the left upper thyroid lobe (Figures 3A, B). Ultrasound scan of parathyroid glands also showed a hypoechoic nodule in the lower posterior part of the right thyroid lobe (3.1 cm×0.9 cm) and a hypoechoic nodule in the left posterior lobe (0.93 cm×0.46 cm), suggesting benign nodules that may originate from the parathyroid gland (Figures 3C, D). The 25 (OH)D3 level was 10.1 ng/ml↓, and the Z-scores of BMD in L1-4 were below 2.0.

The patient was intervened by MWA for supplementary therapy after being fully informed of therapeutic efficacy and potential risks. The MWA for bilateral parathyroid glands was guided by intraoperative ultrasound, as previously reported (9). The MWA system (KY-2000) was produced by Canyon Medical Inc. (Nanjing, China). Briefly, a total of 78 ml of normal saline was injected and maintained surrounding the parathyroid adenoma to create a barrier that prevents thermal damage to the trachea, esophagus and recurrent laryngeal nerve. The ablation antenna was inserted into the parathyroid lesion through previously determined path, and MWA was initiated at 35 W output power. The operation was sustained until the entire gland was hyperechoic (Figures 3E, F). After the ablation, color Doppler ultrasound and contrast-enhanced ultrasound were performed to confirm that no blood flow in the nodule and remaining lesions (Figures 3G, H). The MWA procedure lasted 170 s, and intraoperative heart rate, blood pressure and blood oxygen level were 77 beats/min, 136/79 mmHg and 79%, respectively. The patient only complained of mild pain. PTH level immediately returned to the normal at 10 min postoperatively, and remained normal at 20 min, 4 h, 24 h, 1 month, 2 months, 3 months, 4 months, 7 months and 8 months postoperatively, suggesting the complete remission of

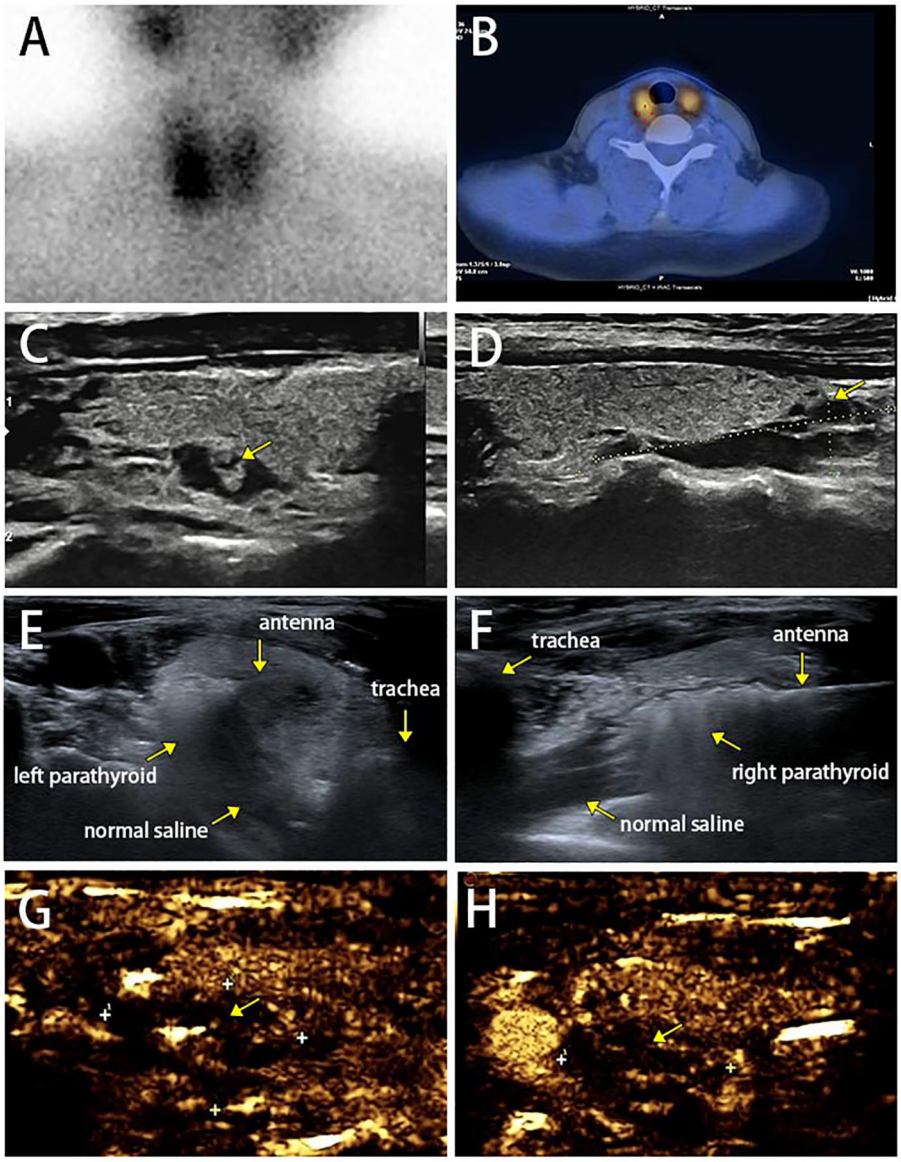

FIGURE 3
(A, B) Dual-phase 99mTc-MIBI parathyroid scan on parathyroid glands with three focal uptakes. **(C, D)** Ultrasound scan of parathyroid glands. **(E, F)** Complete hyperechoic area in the parathyroid glands indicated a complete ablation. **(G ,H)** Postoperative contrast enhanced ultrasound for parathyroid glands did not show blood flow in the remaining lesions.

hyperparathyroidism (Figure 4, Supplementary Table 1). The patient developed hypocalcemia at 1 month postoperatively due to the irregular supplement of vitamin D and calcium. Serum calcium and PTH levels both returned to the normal after treatment. Postoperative adverse events like obvious hoarseness and hemorrhage were not reported.

Discussion

MEN1 is a rare syndrome of an autosomal dominant inheritance pattern, which is caused by germline mutations of the *MEN1* gene on chromosome 11q13 (10). The *MEN1* gene, as a tumor-suppressor, encodes menin that regulates gene expressions and cell proliferation by selectively mediating chromatin remodeling (11). Clinical syndromes of MEN1 include PHPT, pancreatic neuroendocrine tumors, and anterior pituitary adenomas. Up to 88-97% of MEN1 patients suffer PHPT due to parathyroid hyperplasia and/or adenoma (1). The incidence of multiple adenomas or hyperplasia in patient with non-MEN1-related PHPT is as low as 7%, while that of involvement of two or more parathyroid glands by MEN1-related PHPT rises significantly to 56% (2).

Currently, surgery is preferred for MEN1-related PHPT. Except for parathyroid malignancies, MEN1-related PHPT is the trickiest in all parathyroid diseases. The rate of persistent or recurrent PHPT ranges 14-69% (3, 4), and the rate of recurrent hypercalcemia is up to 50% at 8-12 years postoperatively (5). Moreover, the incidence of postoperative permanent hypoparathyroidism reaches 50% (3, 4).

Subtotal parathyroidectomy (SPX, removal of 3-3.5 glands) +bilateral cervical thymectomy, total parathyroidectomy (TPX) +bilateral cervical thymectomy+autotransplantation, and less-than-subtotal parathyroidectomy (LPX) are the three most common surgical procedures for MEN1-related PHPT (3). TPX serves as the only curative procedure for MEN1-related PHPT. However, permanent hypoparathyroidism following TPX is a much severer complication than recurrent PHPT. At present, effective methods to assess the viability of autotransplanted parathyroid glands are scant. SPX is an alternative to TPX (12). It is reported that the incidence of permanent hypoparathyroidism following SPX ranges 0-40%, which has not been improved compared with that of TPX (13, 14). A latest meta-analysis revealed that the relative risk of TPX-induced long-term hypoparathyroidism is significantly higher than that of SPX (RR=1.61; 95%CI[1.12-2.31], P=0.009) (15). LPX can reduce the incidence of postoperative permanent hypoparathyroidism, and enhance the quality of life (16, 17). Through literature review, the recurrence rate of PHPT in patients with MEN1-related PHPT after TPX ranges 0-60% (3, 18–20). Only one randomized control trial has compared SPX and TPX in 32 MEN1 patients. No significant difference in the recurrence rate is identified (24% vs. 13%, P=0.66) (21). Nevertheless, the recurrence rate of PHPT at 19 and 26-28 months of single gland resection (SGE) is 100% (3, 4, 20, 22–24), and the recurrence-free interval after SGE is significantly shorter than that of TPX or SPX (P=0.036) (24). A systematic review and meta-analysis compared the recurrence rate of PHPT after SPX and LPX in patients with MEN1-related PHPT, finding that the risks of recurrence, persistence of hyperparathyroidism, and reoperation for hyperparathyroidism after LPX are all significantly higher than those of SPX (15).

Thus, Optimal therapeutic strategies for MEN1-related PHPT that not only possess an acceptable efficacy but also prevent the recurrence and postoperative hypoparathyroidism remain inconsistent. Moreover, the initial time point for parathyroidectomy and the indications of unilateral debridement to young patients with MEN1-related PHPT are controversial (25). In the present case report, the patient was immediately given to the single parathyroidectomy after the diagnosis of MEN1, which remarkably increased the risks of persistent PHPT and reoperation. It is reported that the postoperative persistent PHPT and hypercalcemia in patients with MEN1-related PHPT are significantly linked with anxiety, depression, fatigue, and decreased social function, all deleterious to the quality of life (26).

Current therapeutic strategies for recurrent MEN1-related PHPT include reoperation, EA and medication of calcimimetics (cinacalcet). Reoperation for PHPT largely increases the risks of recurrent laryngeal nerve palsy and permanent hypoparathyroidism (27). For patients with recurrent MEN1-related PHPT who do not meet surgical indications or refuse to be operated, cinacalcet can only maintain normal ranges of serum calcium and PTH, not

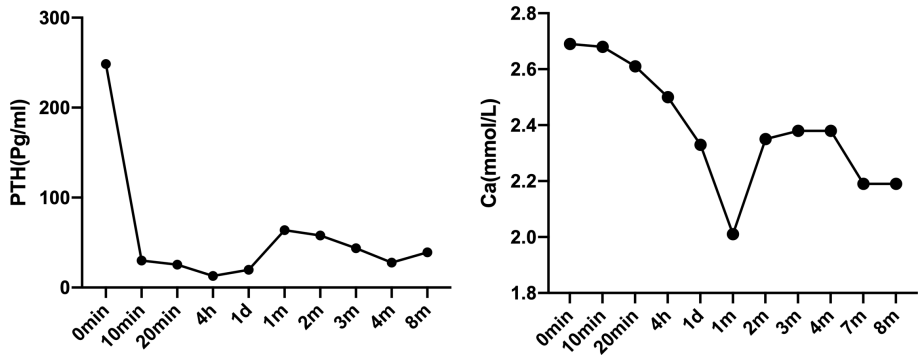

FIGURE 4
Serum PTH and calcium levels before and after ultrasound-guided MWA. MWA, microwave ablation.

reduce the risks of complications like fractures and kidney stones (28).

EA is a minimally invasive procedure that is widely applied to patients with non-MEN1-related PHPT (6, 7), showing a high response rate in previous case reports (7, 29). In a prospective study involving 39 patients with inoperable parathyroid adenomas treated with EA, there are 8 (20.5%), 4 (10.3%) and 1 patient (2.6%) receiving 2, 3 and 4 injections, respectively. After 1-month treatment, 46% of them have improved serum PTH and calcium levels, which increases to 84.5% at 1-year follow-up. No severe complications are reported (30). Veldman et al. performed a total of 41 times of EA to 22 patients with residual and recurrent MEN1-related PHPT in 2008 (31). Among them, 82% of patients with initial hypercalcemia successfully return to the normal range of serum calcium or develop hypocalcemia after EA, and no severe complications like permanent recurrent laryngeal nerve injury are reported. Persistent hypocalcemia is only observed in one patient at 12 months postoperatively. The incidence of hypoparathyroidism after EA is 4.5%, which is lower than that in patients with recurrent MEN1-related PHPT after reoperation. Singh et al. assessed the safety and efficacy of EA on patients with recurrent PHPT and MEN1 diagnosed at Mayo Clinic from 1977 to 2013, including 37 patients for 80 times of EA (123 ethanol injections). A normal range of serum calcium is observed after 54 (73%) times of EA, which persists for an average of 24.8 months. Six (8.1%) patients develop postoperative hypocalcemia, and only 4 (5%) suffer the transient hoarseness (32).

Thermal ablation, including MWA, RFA, LA and HIFU, has been applied to treat PHPT, but never MEN1. It is reported that the volume reduction rate (VRR) of PHPT after MWA has considerably reached 79.8-100% (33), and the cure rate, which is defined as the recovery of serum calcium and PTH, ranges 80.0-100.0% (34, 35). The therapeutic efficacy of MWA on PHPT is comparable to that of surgery. The success rate of MWA in the treatment of PHPT is low in some reports, ranging 62.5-63.6% (9, 36). In addition, the incidence of complication of MWA (6.7%) is lower than that of surgery (35). In our previous study, we assessed PTH, serum calcium and VRR in 20 PHPT patients treated with ultrasound-guided MWA from May 2019 to March 2021, and the technical and clinical success rates were 100% and 63.6%, respectively (9). All PHPT-related symptoms were cured after MWA, and severe complications like permanent nerve damage and permanent hypoparathyroidism were not reported. In the present case report, the patient's serum calcium and PTH recovered immediately after ultrasound-guided MWA. However, postoperative transient hypocalcemia occurred, due to the lack of timely supplementation of vitamin D and calcium, but subsided after a supplementation therapy. The patient has been followed up for closely monitoring serum calcium and PTH. Therapeutic efficacy of EA is linked with the injection method, injection range and ethanol dosage, which usually achieves an acceptable outcome by multiple injections after postoperative evaluations (30, 32). Theoretically, the safety and efficacy of MWA are higher than those of EA, which may be attributed to the complete destruction of the thyroid glands.

MEN1 may bring with other tumors, including adrenal tumor, gastric tumor, skin tumor, subcutaneous tumor, and recently reported breast cancer. Imaging evidence for pituitary tumor in this patient lacked, and corresponding treatment for elevated prolactin and growth hormone levels was not given. In addition, the possibility of breast cancer was not assessed. The patient was postoperatively followed up for less than half a year, and she was still being followed up to analyze long-term efficacy of our treatment.

Conclusion

Genetic testing of *MEN1* gene and screening of other neuroendocrine tumors were performed for this patient, due to the development of multiple parathyroid adenomas. Surgery is the first-line treatment for MEN1-related PHPT, while postoperative recurrence and reoperation rates are relatively high. Ultrasound-guided MWA is a promising option for MEN patient with recurrent PHPT. A large-scale study with a long-term follow-up is needed in the future, aiming to assess the long-term efficacy and safety of MWA on recurrent PHPT in MEN1 patients.

Patient perspective

After I was diagnosed with MEN1, I searched related medical knowledge to understand what disease it was and find what treatment would be the best. After undergoing pancreatic surgery, I was further confirmed to have hyperparathyroidism. The first ECT revealed a parathyroid adenoma on the right side of the neck. Then I turned to an experienced surgeon, but only had this parathyroid lesion removed. Unfortunately, soon after surgery, it found that parathyroid hormone and blood calcium did not return to normal. Before Dr. Xu performed microwave ablation for me, I was informed that thermal ablation had been used for the treatment of hyperparathyroidism; however, there is still no report of MEN1 complicated with hyperparathyroidism receiving thermal ablation. Based on his experience in microwave treatment of parathyroid glands and the current literature of EA treatment for MEN1 hyperparathyroidism, he believed that these two parathyroid lesions could be destroyed by microwave ablation to restore parathyroid function.

The microwave ablation process was generally smoother and safer than I thought, except for minor pain and neck swelling. Postoperative monitoring of parathyroid hormone and serum calcium found that both returned to normal quickly. After the operation, I also developed tetany. Treated with vitamin D and calcium supplements, these symptoms were relieved. I hope my experience can help those MEN1 patients. I also hope that doctors can carry out similar research to find a treatment method with less trauma and better efficacy for patients with MEN1 complicated with primary hyperparathyroidism.

Data availability statement

The data presented in this study will be made available by the authors upon request, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Patient management: XHa, XHu, YtZ, GC. Performing MWA: SX. Data collection: ZL, XHa, LX. Writing manuscript: ZL. Writing review and editing: CL, YzZ, SX. Supervision: SX, CL. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1175377/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Genetic screening of the *MEN1* gene in the proband and her relatives. The arrow indicates the mutation c.1520delG>T (p.G507Afs*52) in exon 10 of the *MEN1* gene. **(A)** the proband. **(B)** the proband's son. **(C)** the proband's nephew.

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Surgical treatment of tertiary hyperparathyroidism: does one fit for all?

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Background: Tertiary hyperparathyroidism (3HPT) is defined as a condition of excessive autonomous excretion of intact parathyroid hormone (iPTH) with persistent hypercalcemia (>10.5 mg/dL) that lasts for more than 12 months after a successful kidney transplantation, in the context of a long course secondary hyperparathyroidism (2HPT). The chronic high levels of iPTH cause a worsening of graft function, accompanied by systemic symptoms of hypercalcemia. The only curative therapy is parathyroidectomy (PTX). It remains unclear whether total parathyroidectomy with autotransplantation (TPTX-AT) or subtotal parathyroidectomy (SPTX) lead to better outcomes.

Aims: The aim of this retrospective, single-institution cohort study is to evaluate the rate of persistent or recurrent disease and postoperative calcium/iPTH disturbances in patients treated with TPTX-AT or SPTX for 3HPT.

Methods: A single-center retrospective analysis of 3HPT patients submitted to TPTX-AT or SPTX between 2007–2020 with at least 24 months follow-up was conducted. The outcome parameters included persistence/recurrence of disease, incidence of transitory hypocalcemia, and temporary/permanent hypoparathyroidism.

Results: A cohort of 52 patients was analyzed and divided in two groups: 38 (73%) were submitted for TPTX-AT, and 14 patients (27%) were submitted for SPTX. The TPTX-AT population showed lower plasmatic calcium concentrations compared with the SPTX group during the entire follow-up period ($p<0.001$). There were eight cases (21%) of transitory hypocalcemia in the TPTX-AT group and none in the SPTX group, with $p=0.065$. Two cases (5%) of temporary hypoparathyroidism occurred in the TPTX-AT group and none in the SPTX group, with $p= 0.530$. There were no cases of permanent hypoparathyroidism and no cases of persistent disease. No statistical difference was assessed for the recurrence of 3HPT between the TPTX-AT group and the SPTX group (N=1, 3% vs N=1, 7%) ($p=0.470$).

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Conclusion: No significative difference was registered between the TPTX-AT and SPTX groups in terms of persistence/recurrence of disease, incidence of transitory hypocalcemia, and temporary/permanent hypoparathyroidism. Mean calcium levels iPTH values were statistically lower among the TPTX-AT group compared with the SPTX group while remaining always in the range of normality.

KEYWORDS

tertiary hyperparathyroidism, renal transplant, subtotal parathyroidectomy, total parathyroidectomy with autotransplant, hypercalcemia

Introduction

Tertiary hyperparathyroidism (3HPT) represents a pathological condition, usually subsequent to a long course secondary hyperparathyroidism (2HPT) that persists after successful renal transplantation (RTX). The incidence of 3HPT stands at about 20% in grafted patients and the need for surgical treatment occurs in 1–5% (1). The tertiary form represents 1.5–2% of all hyperparathyroidism cases; the female to male ratio is 4:1 and incidence peak occurs at 54 ± 15 years (2).

All 3HPT patients show persistent elevated plasmatic intact parathyroid hormone (iPTH) and plasmatic calcium (pCa) concentrations not explained by calcium carbonate or calcitriol supplementation (3). Nodular hyperplasia is the result of prolonged stimulation of parathyroid glands in chronic kidney disease (CKD) for hypocalcemia, low calcitriol values, and high levels of phosphate. Autonomization due to the nodular parathyroid degeneration causes iPTH oversecretion (4).

Patients with 3HPT usually complain of joint or bone pain, nephrolithiasis, vascular or soft tissue calcification, nephrocalcinosis, and fractures; gastro-duodenal ulcers, acute pancreatitis, and weight loss are also reported (5, 6).

Abnormally enlarged parathyroids can be detected with neck ultrasonography color Doppler imaging (US-CD) or sestamibi scanning (Tc-99m sestamibi SPECT-CT) evaluation. US-CD is affordable for high-weight glands (>1,000 mg), while sestamibi scanning is more reliable for smaller hyperplastic glands. Combination of the techniques allows more precise localization, even if in case of ectopic implants. In case of discordant results, four dimension computerized tomography (CT-4D) can be used (7).

Tertiary Hyperparathyroidism (HPT) pathogenic pathways and long-term implications in transplanted populations are not fully understood because of the lack of extended surgical series. However, a decreased renal function is known to be related to long course hypercalcemia and hypercalciuria with a higher risk of fractures and kidney failure (8–10).

Medical therapy with calcimimetics is used to control hypercalcemia but it is associated with low hyperparathyroidism (HPT) regression rates and poor amelioration of the low bone mineral density (BMD) linked to the increased risk of fractures. Nowadays, as reported in a recent review by Dulfer RR, parathyroidectomy (PTX) represents the definitive curative treatment of 3HPT with higher cure rates and lower complications compared with chronic medical therapy. PTX can indeed normalize hypercalcemia and hypophosphatemia and may have beneficial effects on BMD (11).

Indications for PTX are patients with hypercalcemia that persist after 12 months from the RTX, HPT-related clinical manifestations, or pathological bone pain/fractures due to severe osteopenia (12, 13). Although there is a lack of shared operative endpoints, an iPTH intraoperative drop >50% from the preoperative value can be considered the main goal.

Up to now, two surgical strategies are widely accepted: total parathyroidectomy with autotransplantation (TPTX-AT), which is resection of all four parathyroid glands and the normal parathyroid remnants' implantation (30–50 mg) into the subcutaneous/muscular tissue of the forearm; and subtotal parathyroidectomy (SPTX), with the asportation of three parathyroid glands and 7/8 of the fourth one, that appears macroscopically normal,preserving 30–50 mg of well vascularized parenchyma (14).

No large data collection of 3HPT cases comparing the outcomes of TPTX-AT and SPTX are currently available. The aim of this retrospective, single-institution cohort study is to evaluate the rate of persistent or recurrent disease and postoperative calcium/iPTH disturbances in patients treated with TPTX-AT or SPTX for 3HPT.

Materials and methods

We retrospectively analyzed 52 patients affected by 3HPT and treated with TPTX-AT or SPTX between 1 January 2007 and 31 December 2020 at our endocrine surgery center, with at least 24-months postoperative follow-up. Patients older than 18 years submitted to successful RTX with a previous diagnosis of 2HPT and who developed 3HPT with surgical indication for PTX were enrolled in the study. All cases had a history of hemodialysis (graft or tunneled catheter). No cases of peritoneal dialysis were registered. All patients were finally elected to surgery following a multidisciplinary discussion.

Hypercalcemia (pCa > 10.5 mg/dL), elevated iPTH values (normal range 14–65 pg/mL), or symptomatic calcium metabolism alterations (e.g., bone and joint pain, calciphylaxis, and osteodystrophy or pathological fractures) refractory to medical

treatment represented our surgical indications. All patients with previous history of neck surgery for benign or malign thyroid/parathyroid disorders were excluded from the study architecture.

All patients were studied with preoperative US-CD or Tc-99m sestamibi SPECT-CT. All cases of unclear parathyroid localization were submitted to 4D-CT evaluation.

According to the literature, we define TPTX-AT as excision of all four parathyroid glands and the autotransplantation of 30–50 mg of normal-like parathyroid fragments into the subcutaneous forearm tissue. The asportation of three parathyroid glands and 7/8 of the most normal one preserving 30–50 mg of well vascularized parenchyma was defined as SPTX. Thymectomy was performed in each surgical treatment and any ectopic parathyroid tissue previously identified was removed. We decided to transplant the parathyroid remnants into the subcutaneous forearm tissue in order to perform an easier asportation in case of pathological degeneration (15). All parathyroids underwent histological evaluation; nodules' dimension (length of major axis) and weight were reported.

All patients were accurately informed about the two different surgical approaches and their peculiarity in terms of perioperative and long terms management.

All patients received intravenous suppletive calcium therapy during hospitalization and oral calcium carbonate and calcitriol at discharge.

Diagnosis of persistent and recurrent disease was defined as iPTH > 300pg/mL (16) and/or PTH drop < 50% from preoperative level and/or pCa > 10.5 mg/dL within (persistent) or after (recurrent) 6 months from the PTX. Equally, diagnosis of temporary or permanent hypoparathyroidism was defined by the presence of an iPTH level < 13 pg/mL within or after 6 months. After surgery, all patients were treated with calcium supplementation for a minimum of 4 weeks; longer treatment was administered based on periodic plasmatic calcium re-evaluations. Transitory hypocalcemia was defined by postoperative pCa < 8.5 mg/dL with a resolution within 12 months.

Clinical serial follow-up evaluations were performed for a minimum of 24 months: iPTH and pCa assessment were registered each time.

Statistical analyses

Data analysis and management were performed using IBM® SPSS® Statistics 20 for Windows® software. A probability value of p < 0.05 was considered to be statistically significant. The normality of variables was tested using the Shapiro–Wilk method for normal distributions. All continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as numbers (percentage). Fisher's exact test was used for the comparison of categorical data. The Mann–Whitney U test was performed to determine differences between groups.

Results

Population demographics

Between January 2007 and December 2020, a total of 52 patients were submitted to surgical treatment for 3HPT. The mean age was 53 ± 7 years and 26 (50%) were females. The mean time of hemodialysis before RTX was 61.30 ± 23.00 months and surgical treatment of 3HPT was performed after 56.56 ± 68.22 months from the RTX. Thirty-eight (73%) patients had TPTX-AT and 14 (27%) had SPTX. No concomitant thyroidectomies were performed among the two groups due to the absence of both preoperative and intraoperative indications.

Data of each group were collected and compared: no significant differences were registered in terms of sex, age, and time from RTX to PTX (p=0.071, p=0.378, p=0.06, respectively). The mean period of hemodialysis was longer among the TPTX-AT group (64.29 ± 26.29 months) compared with the SPTX group (53.21 ± 4.00 months), with p=0.016. In Table 1, the cohort's demographic distribution is reported.

Perioperative outcomes

Calcium assessment was evaluated before PTX and at patients' discharge with no significant differences among the two groups (p=0.39, p=0.08), with the drop in percentages reported in Table 2. The mean preoperative iPTH value was higher in the TPTX-AT group (751.21 ± 678.24 pg/mL vs 455.43 ± 181.26), with p=0.018. In addition, the iPTH percentage drop at 10 minutes (') after parathyroidectomy was greater among the TPTX-AT group (92.91 ± 5.02% vs 85.85 ± 5.95%; p<0.001). Coherently, iPTH values at 10 minutes (') after parathyroidectomy were lower after TPTX-AT (35.08 ± 21.49 pg/mL vs 61.93± 27.07 pg/mL; p=0.003).

TABLE 1 Demographic characteristics.

	Total	TPTX-AT	SPTX	P Value
N (%)	52	38 (73)	14 (27)	
Age, y	53 ± 7	54 ± 7	50 ± 7	0.07
Sex, female (%) male (%)	26 (50) 26 (50)	20 (53) 18 (47)	6 (43) 8 (57)	0.38
Duration of dialysis (m)	61.3 ± 23	64.29 ± 26.29	53.21 ± 4	0.02
Time from Tx to PTX	56.56 ± 68.22	45.79 ± 62.11	85.79 ± 77.58	0.06

Data collection: Mean ± SD. Two-sided Chi-square or Student's t test were used.
TPTX-AT, total parathyroidectomy with autotransplantation; SPTX, subtotal parathyroidectomy; Tx, renal transplantation; PTX, parathyroidectomy.

10.3389/fendo.2023.1226917

TABLE 2 Perioperative results.

	TPTX-AT	SPTX	P Value
Preop pCa (mg/dL)	10.99 ± 0.50	11.12 ± 0.43	0.39
Preop iPTH (pg/mL)	751.21 ± 678.24	455.43 ± 181.26	0.02
Post 10' iPTH (pg/mL)	35.08 ± 21.49	61.93 ± 27.07	<0.001
Post 10' iPTH drop (%)	92.91 ± 5.02	85.85 ± 5.95	<0.001
Postop pCa (mg/dL)	8.68 ± 0.91	9.01 ± 0.40	0.08
Postop pCa drop (%)	20.91 ± 8.52	18.81 ± 5.24	<0.001
Histology Diffuse (%) Nodular (%)	4 (11) 34 (89)	4 (29) 10 (71)	0.12
Nodules dimension - major axis (cm)	1.30 ± 0.44	1.11 ± 0.51	0.18
Nodules weight (g)	1.21 ± 0.53	1.16 ± 0.47	0.27

Data collection: Mean ± SD or count (percentage). Two-sided Chi-square or Student's t test were used.
TPTX-AT, total parathyroidectomy with autotransplantation; SPTX, subtotal parathyroidectomy; iPTH, intact parathyroid hormone.

In our cohort, supernumerary glands were found within the thymus in two cases, one in each study group, with an incidence of 7% in the SPTX group and of 3% in the TPTX-AT group (p=0.67). No significant differences were found in terms of histology, dimension, and weight between the two groups, as shown in Table 2.

Postoperative and long-term follow up

All 52 patients had a complete 24-month follow-up data collection. The TPTX-AT population showed statistically significant lower pCa levels than the SPTX group during the entire 24-month (6-9-12-18-24 months) follow-up period (p<0.001), as reported in Table 3 and Figure 1. On the other side, although iPTH levels were persistently inferior among the TPTX-AT group (Table 3), a significative p value was registered only at 6 and 9 months (p<0.001; p=0.031). Eight cases (21%) of transitory hypocalcemia were seen in the TPTX-AT group; none appeared in the SPTX group (0%), with a p value close to statistical significance (p=0.065). A higher 10 minutes (') after parathyroidectomy iPTH percentage drop was evident in all these eight cases compared with the residual population values (95.59 ± 2.21% vs 90.18 ± 6.23%) with p<0.001.

Performing specific analysis of the population affected by temporary hypoparathyroidism or transient hypocalcemia, we found that patients with hypocalcemia had lower preoperative calcium levels (10.8 ± 0.4 mg/dL) compared with the rest of population (11.0 ± 0.5) with p<0.001. There was no statistic correlation between preoperative PTH levels and duration of dialysis. Concerning patients with temporary hypoparathyroidism, they were found to have lower preoperative PTH (439.0 ± 12.7 vs 778.1 ± 693.4; p=0.013). There was no statistic correlation between preoperative PTH levels and duration of dialysis.

TABLE 3 Long-term follow-up results.

	TPTX-AT	SPTX	P Value
6 months iPTH (pg/mL)	28.76 ± 9.57	48.64 ± 9.57	<0.001
6 months pCa (mg/dL)	9.12 ± 0.72	9.81 ± 0.42	<0.001
9 months iPTH (pg/mL)	33.29 ± 9.17	75.00 ± 64.33	0.03
9 months pCa (mg/dL)	9.24 ± 0.51	9.90 ± 0.44	<0.001
12 months iPTH (pg/mL)	42.77 ± 24.77	85. 36 ± 86.00	0.09
12 months pCa (mg/dL)	9.39 ± 0.39	9.95 ± 0.35	<0.001
18 months iPTH (pg/mL)	40.50 ± 27.11	83.71 ± 82.47	0.08
18 months pCa (mg/dL)	9.52 ± 0.44	10.05 ± 0.34	<0.001
24 months iPTH (pg/mL)	42.21 ± 27.84	88.00 ± 85.45	0.07
24 months pCa (mg/dL)	9.49 ± 0.43	9.98 ± 0.34	<0.001

Data collection: Mean ± SD. Two-sided paired t test was used.
TPTX-AT, total parathyroidectomy with autotransplantation; SPTX, subtotal parathyroidectomy; iPTH, intact parathyroid hormone.

At the end of the follow-up period, no cases of hypocalcemia were registered in both groups. Two cases (5%) of temporary hypoparathyroidism were found among the TPTX-AT population while no cases (0%) were registered in the SPTX group (p=0.530). Among both groups, there were no cases of permanent hypoparathyroidism. No cases of persistent disease were found in each cohort. No statistical difference was assessed for the recurrence of 3HPT between the TPTX-AT group and the SPTX group (N=1, 3% vs N=1, 7%) (p=0.470). In this context, particular interest is linked to the accuracy rates of localization preoperatory procedures, with the reference standard based on results of surgical exploration and histopathological examination. US-CD sensitivity was 80% while Tc-99m sestamibi SPECT-CT was able to localize pathologic glands in 82% of cases; 4D-CT was particularly useful to solve localization doubts, with a sensitivity of 83%.

The incidence of the three specific recurrence criteria among the two groups was not associated with a significant p value (Table 4).

Furthermore, using a simple linear regression applied to our cohort, a negative correlation was found between length of dialysis treatment and lower pCa levels during the follow-up period (Figure 2). In addition, through multiple regression analysis, we found that the duration of dialysis did not impact the chosen surgical approach, related to pCa values at each follow-up re-evaluation (Table 5).

Discussion

Nowadays, 3HPT remains an uncommon pathological condition that, after failure of medical therapy, requires surgery for definitive curative approach in patients with symptoms of hypercalcemia. Parathyroid asportation aims to normalize pCa and iPTH levels. Owing to the lack of multicentric randomized trials and the low incidence of disease, at this moment, there is no clear consensus about which of two most employed techniques (SPTX or TPTX-AT) allow better outcomes.

10.3389/fendo.2023.1226917

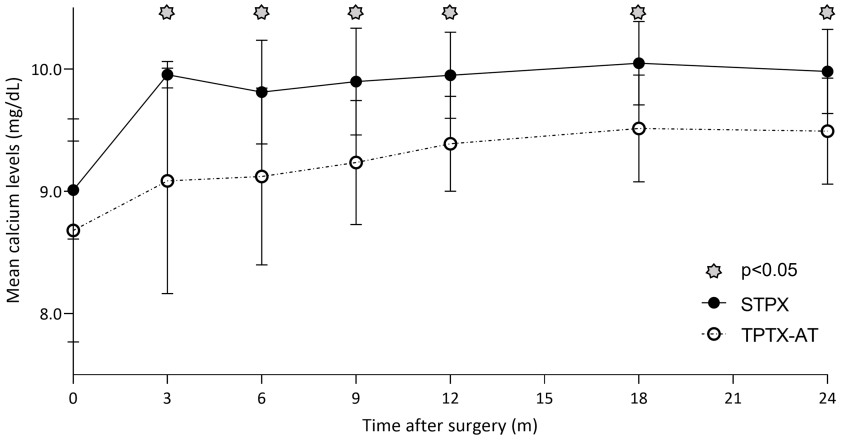

FIGURE 1
Although mean pCa levels were persistently inferior in the TPTX-AT group vs the SPTX group during the entire 24-month follow-up period, these values remained always in the range of normality.

After a complete data assessment, we decided to stratify our population on laboratoristic findings registered preoperatively and during the whole follow-up period, primarily in order to investigate the rates of persistence/recurrence of disease after the two surgical treatments. Different outcomes are taken into consideration and often not all of them are included in the same study among the available literature. Thus, in this study, to be as inclusive as possible, the diagnosis of persistent and recurrent disease was defined considering multiple items: plasmatic iPTH concentration, percentage of iPTH drop, and pCa levels registered within or after 6 months from PTX.

Thanks to the analyses of the three items previously mentioned, we found no persistence of disease equally in both groups, demonstrating the superimposable rate of cure between the different surgical approaches.

According to Gasparri et al., 2001, our incidence of recurrent disease was 3% after TPTX-AT and 7% after SPTX, with no statistically significative differences obtained by the comparison of each of the three items (17). These outcomes could be potentially explained by the surgeon's expertise in facing different preoperative and intraoperative situations and choosing the most suitable strategy to reach a superimposable disease-free result. According to the Miami Criteria, obtaining an iPTH drop >50% is capable of predicting postoperative eucalcemia (18). Furthermore, as explained by several authors, an intraoperative iPTH drop higher than 80% of the basal value can bring a dramatic reduction of recurrences (19).

It appears interesting that in our study the percentage drop obtained in both cohorts was much higher than 80% and this could be connected to our low recurrences rates. Moreover, even if no statistical differences were registered among the two groups in terms of recurrences, in our series it appears significant that the percentage drop in the TPTX-AT population is five percentage points higher than in the SPTX value.

Therefore, even if nowadays is not possible to define the best surgical approach by linking lower recurrences to an higher iPTH drop, it should be considered as fruitful field for future research.

The wide range of ectopic parathyroid localization is known to be the cause of a low curative rate and reappearance of disease; in particular, the thymus is one of the most frequent ectopic sites. In our surgical series, all patients were submitted additional contemporaneous thymectomy and this could be further linked to a good response in terms of cure and recurrence rates (20).

While some authors have documented that more frequent hypocalcemia is linked to TPTX-AT (21), TPTX-AT patients, the prevalence of transitory hypocalcemia appears to be tending towards statistical significance (21% vs 0%, p=0.065).

In this context, it appears interesting to underline that although mean pCa values were persistently inferior in the TPTX-AT group vs the SPTX group, these values remained always in the range of normality. It should be taken into consideration that, despite no critical differences being found between the two surgical techniques, TPTX-AT is linked to more extensive manipulation of parathyroid glands that are unbound from their anatomical peduncle of vascularization and thus transplanted to subcutaneous fat tissue. No immediate reprise of function and calcium homeostasis is guaranteed; indeed, in the literature many cases are reported of persistent hypoparathyroidism if inadequate rooting takes over.

TABLE 4 Focused outcomes.

	TPTX-AT	SPTX	P Value
Temporary hypoparathyroidism	2 (5)	0 (0)	0.53
Permanent hypoparathyroidism	0 (0)	0 (0)	/
Transient hypocalcemia (%)	8 (21)	0 (0)	0.07
6 months persistence 3HPT	0 (0)	0 (0)	/
24 months recurrence 3HPT (%) • iPTH > 300 pg/mL • pCa > 10.5 mg/dL • iPTH Drop < 50%	1 (3) • 0 (0) • 1 (3) • 1 (3)	1 (7) • 1 (7) • 1 (7) • 1 (7)	0.470 • 0.269 • 0.470 • 0.470

Data collection: count (percentage). Two-sided Chi-square was used.
TPTX-AT, total parathyroidectomy with autotransplantation; SPTX, subtotal parathyroidectomy; iPTH, intact parathyroid hormone; 3HPT, tertiary hyperparathyroidism.

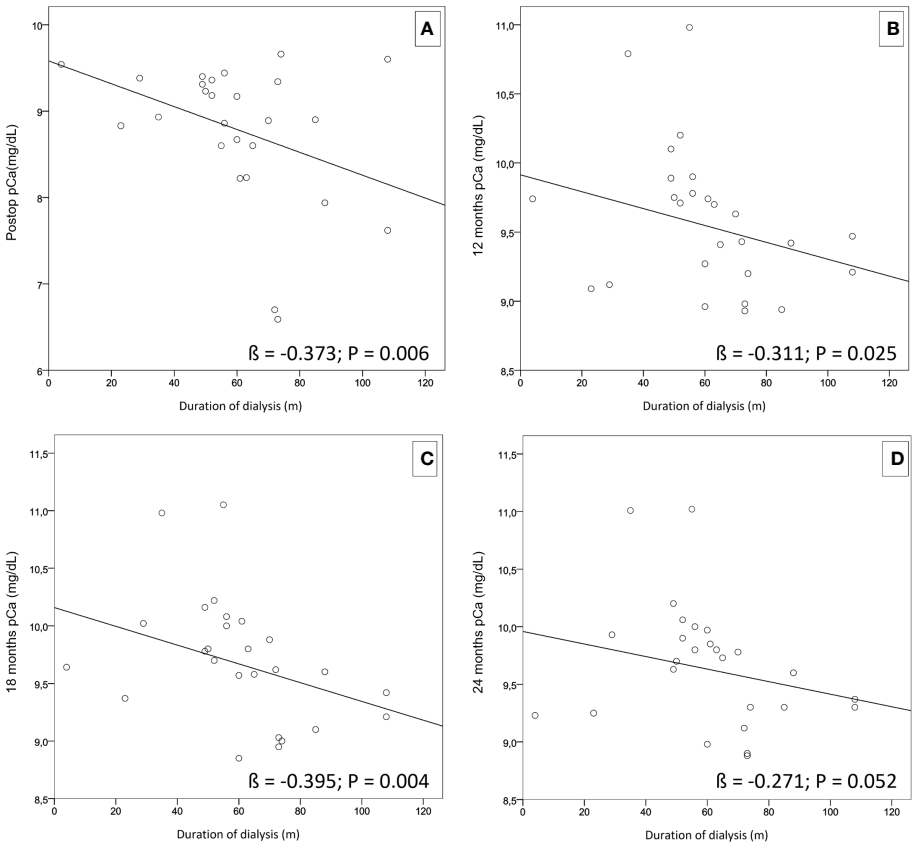

FIGURE 2
Simple linear regressions showing a negative correlation between the length of dialysis treatment and lower pCa levels during the follow-up period. **(A)** (ß = -0.373; p = 0.006). **(B)** (ß = -0.311; p = 0.025). **(C)** (ß = -0.395; p = 0.004). **(D)** (ß = -0.271; p = 0.052).

Furthermore, as known, chronic kidney disease–mineral bone disorder (CKD-MBD) represents a condition that also affect patients with 3HPT. As reported by Wazeri et al., 2019 (6), the development of parathyroid hyperplasia is linked to specific alterations in bone metabolism; indeed, the progression to a nodular hyperplasia, starting from a diffuse form, is developed in a vitamin D hunger state appearance. In the context of end-stage CKD with no functioning kidney parenchyma, a continuous absorption of calcium from the bone, will cronically lead to cortical bone loss. In these patients, as explained by Cartwright et al., 2023 (22), in the postoperative period, the so-called "hungry bone syndrome" may set in and plasmatic calcium homeostasis may not be guaranteed because of the increased calcium absorption by bones.

Literature reports a higher incidence of hypoparathyroidism after TPTX-AT versus SPTX. It is confirmed even in our series in which two cases of hypoparathyroidism after TPTX-AT were described (5% vs 0%) (23).

TABLE 5 Variable impact analysis.

	Duration of dialysis (m)	SPTX	TPTX-AT	P Value	P Interaction
Postop pCa (mg/dL)	≤ 60	9.14	9.19	0.697	0.885
	> 60	8.22	8.35	0.545	
12 months pCa (mg/dL)	≤ 60	9.98	9.52	0.014	0.695
	> 60	9.74	9.31	<0.001	
18 months pCa (mg/dL)	≤ 60	10.05	9.71	0.067	0.364
	> 60	10.04	9.39	<0.001	
24 months pCa (mg/dL)	≤ 60	10	9.67	0.076	0.909
	> 60	9.85	9.38	<0.001	

Data collection: Mean value. Multiple regression was used.
TPTX-AT, total parathyroidectomy with autotransplantation; SPTX, subtotal parathyroidectomy.

Although a complete resolution of the hypoparathyroidism was assessed at 6-month evaluation, the average iPTH levels remained constantly lower at the intraoperative post-dissection dosage and at each re-evaluation measurement in the TPTX-AT group.

Surgical approaches in parathyroid disease underwent relevant modifications in the last few decades. Alongside the well-known total and subtotal parathyroidectomy, other "image-guided" approaches have been developed to allow a more limited glandular excision, for example, the so-called "less than subtotal parathyroidectomy" in which only glands with preoperative or intraoperative pathological features are removed (24).

In the literature, during the past two decades, several experiences of this technique have been reported, principally in the context of a primary hyperparathyroidism, with successful postoperative results that, unfortunately, did not seem to be obtained in the context of Tertiary hyperparathyroidism (THPT) conditions (25).

Indeed, despite apparently good PTH reduction in the immediate postoperative period, persistence and recurrence of disease appeared to be deeply influenced by the insufficient amount of tissue removal (26).

Furthermore, even in presence of macroscopically normal glandular tissue, hyperplastic features are present at histological evaluation, thus, THPT patients should not be eligible for limited resections in the context of an apparent normal glandular morphology in order to avoid rapid recurrences and difficult cervical re-explorations in case of graft deterioration (27).

Lastly, even if total parathyroidectomy without autotransplantation has been described, because of several cases of persistent hypoparathyroidism reported in our first surgical experiences and in the literature too, such procedure has not been performed at our center for 20 years.

As Supplementary Material, a brief literature comparison is shown in Supplementary Table 2.

Conclusions

Although the shared indications for surgical treatment of 3HPT are well defined, no consensus has still been declared about the best surgical approach to PTX and which postoperative outcomes must be primarily taken into consideration.

Nowadays, in the context of 3HPT, the literature accepts different surgical management based on the surgeon's choice and experience (28–33). The results of the postoperative outcomes described by our study embrace this state of the art, allowing well-trained endocrine surgeons to choose between TPTX-AT and SPTX to offer patients a case-specific tailored approach. Since just few cases of this rare condition are treated every year, a collegial expertise can be extremely useful in reaching the more correct work-up for each patient. Therefore, it is our belief that each surgical indication should include an adequate patient's informed interview, a preoperative multidisciplinary staff discussion based on imaging evaluation, and the ability to calibrate the surgical approach considering the intraoperative findings.

The study could be limited by its retrospective monocentric nature, by the lack of randomization, and by the exiguity of sample size. On the other side, the main force of the project is represented by the standardized data collection and the long course follow-up.

The authors aim to encourage further studies on wider populations and cooperative data sharing in order to define the best surgical treatment.

Data availability statement

The raw data used are available from the authors upon request by any qualified researcher.

Ethics statement

According to current Italian Law, the approval of the Ethics Committee for a retrospective observational study is not required. Informed consent was obtained from all patients.

Author contributions

CC, MC, XA, RM, and CG contributed to the conception and design of the work. RM and CG participated in data analysis and text editing. RM, CG, and PG participated in data collection and patients' follow-up. CC, MC, and XA contributed to text revision and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1226917/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Mean iPTH levels after surgery among the two populations. As shown, mean iPTH was lower in the STPX group and a p value < 0.05 was registered at patients' discharge and at 6-9 months follow-up (asterisk labeled).

SUPPLEMENTARY FIGURE 2
Mean calcium levels at preoperative and postoperative (at time of patients' discharge) evaluations. Preop pCa in the TPTX-AT group and the SPTX group (10.99 ± 0.50 vs 11.12 ± 0.43; p=0.39). Postop pCa in the TPTX-AT group and the SPTX group (8.68 ± 0.91 vs 9.01 ± 0.40; p=0.08).

SUPPLEMENTARY FIGURE 3
Mean iPTH levels at preoperative and postoperative (evaluated at 10' after PTX) dosages. Preop iPTH in the TPTX-AT group and the SPTX group (751.21 ± 678.24 vs 455.43 ± 181.26; p=0.02). Post 10' iPTH in the TPTX-AT group and the SPTX group (35.08 ± 21.49 vs 61.93 ± 27.07; p<0.001).

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Recurrent laryngeal never monitoring versus non-monitoring in parathyroid surgery

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Background: Although intraoperative neural monitoring (IONM) is well established in thyroid surgery, it is less commonly analyzed in parathyroid operations. This study presents the results of IONM for primary and secondary hyperparathyroidism surgery.

Methods: We retrospectively assessed 270 patients with primary hyperparathyroidism (PHPT), 53 patients with secondary hyperparathyroidism (SHPT), and 300 patients with thyroid cancer from June 2010 to June 2022 in one hospital in China. The follow-up was 12 months. Demographic, electromyography data from IONM, laboratory, and clinical information were collected. Laryngoscopy was collected from 109 patients with PHPT in whom IONM was not used. All groups were assessed by Pearson's chi-square test and Fisher's exact probability method to verify the relationship between parathyroid size and location, duration of surgery, preoperative concordant localization, laryngeal pain, IONM outcomes, cure rate, and RLN injury. Visual analog scale (VAS) assessed laryngeal pain. RLN outcomes were measured according to nerves at risk (NAR).

Results: The study comprehended 918 NAR, that is 272, 105, 109, and 432 NAR for PHPT, SHPT with IONM, PHPT without IONM, and thyroid surgery control group, respectively. IONM successfully prevented RLN injury ($P<0.001$, $P=0.012$): Fifteen (5.51%) RLNs experienced altered nerve EMG profiles during surgery, and five (1.84%) experienced transient RLN injury in PHPT patients. Five (4.76%) RLNs were found to have altered EMG profiles during surgery, and one (0.95%) RLN had a transient RLN injury in SHPT patients. There was no permanent nerve injury (0.00%) in this series. There was no association between location, gland size, preoperative concordant localization, cure rate, duration of surgery, and IONM ($P>0.05$). Duration of surgery was associated with postoperative pharyngeal discomfort ($P=0.026$, $P=0.024$). Transient RLN injury was significantly lower in patients with PHPT who underwent IONM than in those who did not. Intraoperative neuromonitoring played an effective role in protecting the

recurrent laryngeal nerve (P=0.035). Compared with parathyroidectomy, thyroidectomy had a higher rate of RLN injury (5.32%, P<0.001).

Conclusion: IONM for SHPT and PHPT offers rapid anatomical gland identification and RLN functional results for effective RLN protection and reduced RLN damage rates.

KEYWORDS

primary hyperparathyroidism, secondary hyperparathyroidism, parathyroidectomy, intraoperative neural monitoring, IONM, recurrent laryngeal nerve, morbidity, pain

1 Introduction

Parathyroidectomy (PTX) is an effective treatment for drug-refractory primary hyperparathyroidism (PHPT) and secondary hyperparathyroidism (SHPT) (1, 2). PHPT and SHPT have a high prevalence in China, and the incidence of PHPT and SHPT is increasing every year (3, 4).

Recurrent laryngeal nerve (RLN) injuries occur during PTX (5–11). The prevalence of transient RLN injury is 0.8% to 10.6% (8–11). The probability of permanent RLN injury ranges from 0.0% to 14.0% (8–11).

Although intraoperative nerve monitoring (IONM) is well-established in thyroid surgery, it is less frequently analyzed in parathyroid surgery (12–14). According to the international IONM guidelines, nerve monitoring is recommended in parathyroid surgery, but this suggestion is based on evidence from thyroid surgery, not parathyroid surgery (15).

This study presents the results of IONM in primary and secondary hyperparathyroidism surgery, focusing on surgical success rate, RLN outcomes, size and location of the parathyroid, duration of surgery, and pain compared to patients undergoing surgery without IONM.

2 Materials and methods

2.1 Time frame, patients, and setting

From June 2010 to June 2022, 270 patients with PHPT, 53 SHPT, 300 patients with thyroid cancer treated intraoperatively with IONM, and 109 patients with PHPT who did not receive IONM from the Department of Thyroid Surgery, China-Japan Union Hospital, Jilin University, China.

2.2 Ethics

Study registration number: 20230630016. The study was approved by the Institutional Review Board. Patients or their legal guardians will sign a detailed informed consent form before surgery.

2.3 PHPT and SHPT epidemiology in China

PHPT patients are increasing year by year. The number of patients with asymptomatic hyperparathyroidism is on the rise and has exceeded 50 percent of all patients until now (3). The number of patients with SHPT is increasing year by year, and according to statistics, the prevalence of CKD in China is estimated at 10.8 percent (4).

2.4 Inclusion and exclusion criteria

2.4.1 Inclusion criteria

We analyzed patients operated on for PHPT and SHPT compared with patients operated on for thyroid cancer with IONM and patients operated on for PHPT without IONM. Only patients with pre- (L1) and post-laryngoscopy (L2) were included on the first postoperative day. Patients with or without imaging concordant were included. All patients enrolled were ≥ 18 years old. Reoperation patients and patients with preoperative RLN injury included.

2.4.2 Exclusion criteria

(i) Patients with incomplete data or incomplete follow-up. (ii) Patients with concomitant thyroidectomy. (iii) Patients without L1 and/or L2. (iiii) Tertiary hyperparathyroidism and multiple endocrine neoplasms were excluded.

2.5 Definitions

PHPT was diagnosed by the presence of hypercalcemia and a concomitant elevated or inappropriately normal serum PTH level - specifically, PTH > 20 pg/ml with a serum Ca level of > 2.6 mmol/L. The diagnosis of asymptomatic PHPT (aPHPT) was based on the absence of typical symptoms or signs associated with hypercalcemia; the diagnosis was made incidentally on serum Ca level testing or neck ultrasound (US). SHPT is the release of increased amounts of parathyroid hormone, which is an appropriate response to a low calcium or vitamin D level to try to restore calcium levels to normal. Recurrent SHPT is defined as

PTH <300 pg/ml within 6 months after surgery and PTH >300 pg/ml after 6 months again. Persistent SHPT is defined as PTH consistently >300 pg/ml after surgery. Laboratory tests included serum Ca (reference range, 2.00-2.60 mmol/L), serum phosphate (0.60-1.60 mmol/L), fasting blood glucose (FBS; 3.7-6.0 mmol/L), alkaline phosphatase (AKP; 50-135 U/L), serum creatinine (sCr; 58-133 umol/L), PTH (15-65 pg/mL) and 25-hydroxyvitamin D (25 (OH)D; ≥30 ng/mL). Patients were referred and followed up by their referring endocrinologist.

2.6 Indications for surgery in SHPT patients

Patients with SHPT who undergo surgical treatment are mainly those who have failed medical treatment, whose PTH cannot be controlled within 9 times the normal reference value, and who have complications caused by HPT, or those who are inclined to undergo surgical treatment. The major complications are (1) uncontrolled hypercalcemia or hyperphosphatemia; (2) calcification defense or systemic severe extraosseous calcification; (3) cortical bone fracture; (4) weakened limb muscles and bone or joint pain that affects the quality of life; (5) uncontrolled itching that leads to lesions and/or affects the quality of life; and (6) patients with proximity to renal transplantation at risk of severe post-transplant hypercalcemia (16).

2.7 Preoperative localization examinations

Preoperative localization was performed by cervical ultrasound (US) and 99mTc-labelled sestamibi image. If the localization scans matched, the abnormal gland was identified using a focused minimally invasive approach, and if the scans did not match, standard bilateral neck exploration was performed.

2.8 Intraoperative gland localization

The localization (originating from the right superior, right inferior, left superior, or left inferior parathyroid gland) was determined perioperatively. The superior and inferior parathyroid glands may be very close to each other on a craniocaudal axis, but the typical landmark that was always used was the position of the parathyroid glands and any adenoma relative to the RLN. The upper parathyroid glands typically lie dorsal to the plane of the RLN, while the lower parathyroid glands lie ventral to the plane of the RLN, and in adenomatous enlargement, the migratory pathways of the upper and lower gland adenomas tend to respect this plane.

2.9 Intraoperative PTH

IOPTH values were initially checked after induction of anesthesia. They were then rechecked 30 minutes after surgical removal of the parathyroid gland. A > 50% drop in IOPTH levels 30 minutes after removal was used to confirm the successful removal of the abnormal gland.

2.10 Treatment

Surgical procedures were divided into (a) conventional: bilateral cervical exploration, visualization of all parathyroid glands, and removal of the pathological gland(s). (b) focused by open minimally invasive approach: identification and targeted removal of the gland (s) identified as pathological.

2.11 Variables

Sex, age, BMI, preoperative serum calcium, postoperative serum calcium, preoperative serum phosphorus, preoperative parathyroid hormone (PTH), IOPTH, alkaline phosphatase (ALP), IONM data, laryngoscopy data, parathyroid gland location and size, course of RLN, postoperative paraffin pathology. The most common postoperative complications were recorded (transient or permanent hypocalcemia; unilateral or bilateral paralysis of the vocal cords).

2.12 Grouping method

We analyzed: (a) the effect of IONM on RLN injury in PHPT and SHPT patients with IONM. (b) IONM compared to PHPT patients without IONM. (c) RLN injury rate compared to patients operated on for thyroid cancer in the same study period.

2.13 IONM technique

The RLN was monitored (Nerve Integrity Monitor 3.0 from Medtronic (USA)) according to the "four-step RLN monitoring method" proposed by Chiang et al. (17), i.e., V1, R1, V2, and R2 were recorded. During the surgery, intermittent monitoring was the main method, we continuously monitored the patient's RLN with the IONM when the nerves were dissected. In the event of RLN injuries, we have archived all information, i.e. possible cause of injury, anatomical details of the parathyroid, and anatomical details of the nerve. The operating steps of the IONM are shown in Table 1. V1 and V2 were stimulated without dissection of the carotid sheath.

2.14 RLN follow-up

Intraoperative temporary nerve signal abnormalities were defined as the loss of nerve signal intraoperatively but recovery of nerve signal at the end of surgery. Intraoperative persistent nerve signal abnormalities are defined as the loss of nerve signal

10.3389/fendo.2023.1299943

TABLE 1 Operational steps for IONM.

Operation	Note
IONM Four-Step Approach	
Step 1, V1 signal	A significant EMG signal was obtained by probing the ipsilateral vagus nerve at the level of the inferior pole of the thyroid gland (point B) (proving the successful establishment of the monitoring system). If there is no signal at point B, the vagus nerve is probed at the level of the upper pole of the thyroid gland (point A), and a signal is obtained at point A, confirming the presence of a non-returning laryngeal nerve variant.
Step 2, R1 signal	Before revealing the RLN, use a probe to "cross" the trachea perpendicularly and then parallel to the trachea in the area of its course. Positioning of the RLN and monitoring of the EMG signals after exposure to the RLN
Step 3, R2 signal	Continuous monitoring during dissection of the RLN and real-time comparison of signal changes. After full exposure, the EMG signals are obtained at the nearest end of the exposure.
Step 4, V2 signal	Detection of vagal EMG signals after complete hemostasis in the operative field and before closing the incision.
Signal Interpretation	
R2, V2 signal not significantly attenuated	Functional integrity of the RLN
R2, V2 signal loss	Damage to the RLN during a surgical operation, and explore the nerve's "damage point" to find the cause of the damage

intraoperatively until the end of surgery. Patients with abnormal vocal fold movements were reexamined by laryngoscopy at the second, fourth, and sixth postoperative weeks.

Transient RLN injury is defined as symptoms of neuropraxia resolving within six months. Permanent RLN injury is defined as symptoms of neuropraxia persisting for six months.

2.15 Assessment of postoperative pharyngeal pain

The visual analog scale (VAS) (18) was used to assess the degree of pharyngeal pain experienced by patients on the first day after surgery.

2.16 Pathology

Paraffin pathology was done on all parathyroid glands removed and all pathology reports were recorded in detail.

2.17 Statistical methods

Statistics are for nerves at risk(NAR), not patients.SPSS 27.0 software was used for statistical analysis. Measurement data were expressed as mean ± standard deviation; count data were expressed as frequency and percentage (%). The Kruskal-Wallis rank sum test was used to compare continuous variables, the Pearson chi-square test was used for categorical variables, and Fisher's exact probability method was used to compare theoretical frequencies < 1. $P < 0.05$ was statistically significant, and $P < 0.01$ was statistically significant.

3 Results

3.1 Basic information

3.1.1 Basic population

The study consists of 270 patients with PHPT, 53 SHPT, 300 patients with thyroid cancer treated intraoperatively with IONM, and 109 patients with PHPT who did not receive IONM. Some patients did not use IONM because of financial problems or for their own reasons. See Figure 1.

A higher percentage of female patients (74.4%) than male patients (25.6%) participated in the study with PHPT. The ratio of male to female patients at SHPT was 2.5:1. PHPT and SHPT patients were statistically significantly different in terms of age, preoperative serum calcium, preoperative serum phosphorus, preoperative alkaline phosphatase, preoperative PTH, intraoperative PTH, calcitonin, parathyroid length and duration of surgery ($P < 0.05$). See Tables 2, 3.

3.1.2 Pathology

In the PHPT group, more diseased parathyroid glands were located in the lower thyroid (77.89%) and less than 2 cm (72.28%); surgery lasted less than 1.5 hours in most patients (60.37%). In the SHPT group, 7 ectopic parathyroid glands were found, of which, 2 parathyroid glands were in the carotid sheath and 5 parathyroid glands were in the thymic horn. See Table 2.

Of 285 parathyroid glands in PHPT patients, adenomas were seen in 275 (96.49%), hyperplasia in eight (2.81%), and cysts in two (0.70%). Of 212 parathyroid glands of SHPT patients, adenomas appeared in 200 (96.34%) and hyperplasia in 12 (5.66%). See Table 2.

3.1.3 Follow-up examination

In this study, patients were followed up for 1 year after surgery. We found that: after 1 year, the cure rate of PHPT patients was 99.63% and one patient (0.37%) had recurrence. The cure rate of SHPT was 92.45%, three (5.66%) patients had recurrence and one (1.89%) patient had persistent hyperparathyroidism. See Table 2.

3.1.4 NAR

In the PHPT group, two hundred and seventy-two RLNs were dissected during the procedure. Fifteen RLNs (5.56%) had abnormal RLN signals during the procedure, and five RLNs (1.85%) had abnormal RLN signals at the end of surgery.

In the SHPT group, one hundred and five RLNs were dissected intraoperatively. Five RLNs (9.43%) had abnormal intraoperative RLN signals, and one RLN (1.89%) had abnormal RLN signals at the end of surgery. See Table 2.

10.3389/fendo.2023.1299943

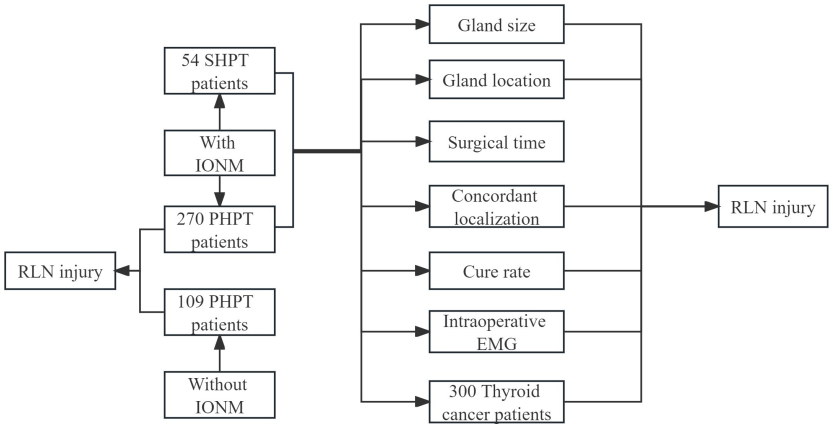

FIGURE 1
Flowchart of different groups for RLN injury analyzing.

3.1.5 Laryngeal examination results

In the preoperative laryngoscopy, we found that three patients who underwent reoperation had their right vocal folds fixed in a paramedian position and were hoarse, including two patients with PHPT and one with SHPT; the other patients had good vocal fold movement and no RLN injury. Laryngoscopy was repeated on the first day after surgery. Five (1.85%, 5/270) PHPT patients had transient RLN injury and one (1.89%, 1/53) SHPT patient had transient RLN injury. Laryngoscopy revealed that the left vocal cord was fixed in the paramedian position in four patients and the right vocal fold was fixed in the paramedian position in two patients. Laryngoscopies were performed every fortnight after surgery in six patients, and six weeks after surgery the movement of the bilateral vocal folds was symmetrical and well closed, without hoarseness or cough.

3.1.6 Surgical procedures

In the 270 PHPT patients with intraoperative use of IONM, 2 patients underwent parathyroidectomy/bilateral exploration and the others underwent unilateral exploration. All PHPT patients without intraoperative IONM underwent parathyroidectomy/unilateral exploration. All SHPT patients (53) underwent total parathyroidectomy (bilateral exploration) combined with bilateral central group lymph node dissection. 300 thyroid cancer patients underwent thyroid lobectomy combined with lymph node dissection. The details are shown in Table 4.

3.2 Relationship between RLN injury and preoperative concordant localization studies

Of the 285 parathyroids in patients with PHPT, a total of 262 (91.93%) parathyroids were localized consistently with the preoperative examination, of which four parathyroids were resected with persistent RLN nerve signal abnormality. Twenty-three (8.07%) parathyroids were localized inconsistently or without clear preoperative localization, and one parathyroid was resected with persistent RLN nerve signal abnormality. Of the 212 parathyroids in patients with SHPT, a total of 173 (81.60%)

TABLE 2 Distribution of the number of different groups of patients with basic information.

Variables	Grouping	Number	Total
PHPT patients			
Gender	Male	69 (25.66%)	270
	Female	201 (74.44%)	
Parathyroid location	Superior parathyroid	63 (22.02%)	285
	Inferior parathyroid	222 (77.89%)	
Parathyroid size	≥2cm	79 (27.72%)	285
	<2cm	206 (72.28%)	
Parathyroid pathology	adenoma hyperplasia cyst	275 (96.49%) 8(2.81%) 2(0.70%)	285
Duration of surgery	≥1.5h	107 (36.63%)	270
	<1.5h	163 (60.37%)	
RLN nerve signals	Normal signal	257 (94.49%)	272
	Temporary nerve signal abnormalities	10 (3.68%)	
	Persistent nerve signal abnormalities	5 (1.84%)	
Follow-up results	Number of cures	269 (99.63%)	270
	Number of recurrences	1(0.37%)	

(Continued)

10.3389/fendo.2023.1299943

TABLE 2 Continued

Variables	Grouping	Number	Total
SHPT patients			
Gender	Male	38 (71.70%)	53
	Female	15 (28.30%)	
Parathyroid location	Superior parathyroid	106 (50.00%)	212
	Inferior parathyroid	99 (46.70%)	
	Ectopic parathyroid	7 (3.30%)	
Parathyroid size	≥2cm	71 (33.49%)	212
	<2cm	141 (66.51%)	
Parathyroid pathology	adenoma hyperplasia	200 (94.34%) 12(5.66%)	212
Duration of surgery	≥1.5h	43 (81.23%)	53
	<1.5h	10 (18.87%)	
RLN nerve signals	Normal signal	100 (95.24%)	105
	Temporary nerve signal abnormalities	4 (3.81%)	
	Persistent nerve signal abnormalities	1 (0.95%)	
Follow-up results	Number of cures	49(92.45)	53
	Number of persistent	1(1.89%)	
	Number of recurrences	3(5.66%)	

parathyroids were localized consistently with the preoperative examination, and one parathyroid was resected with persistent RLN nerve signal abnormality. Thirty-nine (18.40%) parathyroids were localized inconsistently or were not localized definitively preoperatively. Statistical findings: under IONM, there was no relationship between preoperative localization of parathyroids and RLN injury in PHPT patients (P=0.396) and SHPT patients (P=0.523). See Table 5.

3.3 Relationship between glandular location and RLN injury

A total of 285 diseased parathyroid glands were resected in PHPT patients and 212 parathyroid glands in SHPT patients. In IONM, two RLNs had persistent RLN signaling abnormalities after resection of the upper parathyroid gland and three RLNs had persistent RLN signaling abnormalities after resection of the lower parathyroid gland in PHPT patients. One RLN had persistent RLN signaling abnormalities after upper parathyroid resection in SHPT patients. Statistically, there was no association between resection of a differently located parathyroid gland in PHPT (P=0.668) and SHPT patients (P=0.499) and RLN injury with IONM. See Table 6.

TABLE 3 Statistical values of basic patient information and laboratory indicators.

Variables	Statistical values (Mean ± SD)		*P*
	PHPT patients	SHPT patients	
Age(years)	51.59 ± 10.70	46.17 ± 9.732	<0.001
BMI	24.06 ± 7.24	23.02 ± 3.13	0.299
Preoperative serum calcium (mmol/L)	2.90 ± 0.32	2.54 ± 0.20	<0.001
Postoperative serum calcium (mmol/L)	2.29 ± 0.23	2.21 ± 0.35	0.063
Preoperative serum phosphorus (mmol/L)	0.89 ± 0.24	2.50 ± 0.55	<0.001
Preoperative alkaline phosphatase(mmol/L)	214.27 ± 322.77	562.77 ± 511.35	<0.001
Preoperative PTH(pg/mL)	515.57 ± 616.51	2153.10 ± 888.50	<0.001
Intraoperative PTH(pg/mL)	49.72 ± 68.75	176.50 ± 85.05	<0.001
PTH decline rate	0.88 ± 0.09	0.91 ± 0.04	0.226
Calcitonin(pg/mL)	1.10 ± 2.59	12.83 ± 13.90	<0.001
Parathyroid length(cm)	1.86 ± 0.33	1.51 ± 0.51	<0.001
Duration of surgery(mins)	89.4 ± 23.90	107.30 ± 17.62	<0.001

Intraoperative pictures of our center which showed parathyroid glands in different locations with RLN. Figure 2.

3.4 Gland size and RLN injury

The mean diameter of the diseased parathyroid gland in PHPT patients was 1.86 cm; seventy-nine parathyroid glands were ≥2 cm long, of which three (3.80%) RLNs had persistent RLN signaling abnormalities. Two hundred and six parathyroid glands were < 2 cm long, and two (0.97%) RLNs had persistent RLN signaling abnormalities. The mean diameter of the diseased parathyroid gland in SHPT patients was 1.51 cm, with 71 parathyroid glands ≥2 cm in length, of which one (1.40%) RLN had persistent RLN signaling abnormalities, and 141 parathyroid glands < 2 cm in length, without RLN injury. In IONM, RLN injury was not associated with parathyroid size in PHPT (P=0.261) and SHPT patients (P=0.138). See Table 7.

3.5 Cure rate and RLN injury

Of the 270 PHPT patients, all five (1.86%) patients who developed transient RLN damage were from the 269 cured patients. One (2.04%) of the 53 SHPT patients who developed transient RLN damage were from the cured patients. Statistical findings: under IONM, there was no relationship between cure rate, incidence of persistent hyperparathyroidism, recurrence rate, and

10.3389/fendo.2023.1299943

TABLE 4 Specifics of different surgical procedures.

	Parathyroidectomy/ unilateral exploration	Parathyroidectomy/ bilateral exploration	Total	Number of nerves dissected
PHPT patients with IONM	268	2	270	272
PHPT patients without IONM	109	0	109	109
*SHPT patients with IONM	0	53	53	106
	Thyroid lobectomy combined with lymph node dissection	Total thyroidectomy combined with lymph node dissection		
Thyroid cancer patients with IONM	300	0	300	300

*Surgical scope for SHPT patients includes total parathyroidectomy (bilateral exploration) combined with bilateral central group lymph node dissection.

RLN injury in PHPT patients (P=0.931) and SHPT patients (P=0.924). See Table 8.

3.6 Duration of surgery and RLN injury and pharyngeal symptoms

Of the 107 patients with PHPT whose surgery duration was more than 1.5 hours, four (3.73%) patients had temporary RLN injuries, and 91 (85.05%) patients had pharyngeal discomfort. Of the 163 patients with surgery duration of less than 1.5 hours, one (0.61%) patient was observed with transient RLN injury and 120 (73.62%) patients with pharyngeal discomfort. Forty-three patients with SHPT had a surgery duration of more than 1.5 hours, one (2.32%) patient with a transient RLN injury and 40 (90.67%) patients with pharyngeal complaints were observed. In the ten patients with surgery duration of less than 1.5 hours, there was no RLN injury and six patients (60.00%) had pharyngeal discomfort. The statistical results showed that in IONM, the duration of surgery ($\chi2$ = 1.964, P=0.161; $\chi2$ = 0.423, P=0.516) was not the cause of RLN injury and was a factor in postoperative pharyngeal discomfort ($\chi2$ = 4.939, P=0.026; $\chi2$ = 5.106, P=0.024) (see Figures 3A, B. The duration of surgery has a direct correlation with the incidence of postoperative pharyngeal discomfort, with longer surgeries resulting in a higher likelihood of patients experiencing this discomfort. Additionally, those who do experience postoperative pharyngeal discomfort are more likely to report moderate to severe pain. Figures 3C, D.

3.6.1 IONM for RLN injury (1)

With IONM, 15 (5.51%) RLNs had abnormal RLN signals, and only five (1.84%) had abnormal RLN signals at the end of surgery in 270 patients with PHPT. In 53 patients with SHPT, five RLNs (4.76%) had abnormal RLN signals during surgery, and only one RLN (0.95%) had abnormal RLN signals at the end of surgery. The statistical results showed that with IONM, the surgeon recognized the possible contributing factors for intraoperative nerve injury in time and avoided the risk. RLN injury was effectively prevented in PHPT patients (P < 0.001) and SHPT patients (P=0.012). See Table 9.

3.6.2 IONM and RLN injury (2)

To investigate whether IONM can protect RLN, 270 PHPT patients who used intraoperative IONM and 109 PHPT patients who did not use intraoperative IONM were counted. The rates of temporary RLN injury were 1.84% (5/272) and 5.50% (6/109) for both. The rates of permanent RLN injury were 0.00% and 0.92% (1/109), indicating that using IONM during surgery effectively protected against RLN (P =0.013). See Table 10.

TABLE 5 Table of the relationship between parathyroid Concordant Localization and RLN injury.

	Number of examples	Persistent RLN signal abnormalities	Normal signal	χ^2	*P*
Parathyroid of PHPT patients					
Concordant localization	262(91.93%)	4 (1.53%)	258 (98.47%)	0.720	0.396
Discordant or negative localization	23(8.07%)	1 (4.35%)	22 (95.65%)		
Total	285	5 (1.75%)	280 (98.25%)		
Parathyroid of SHPT patients					
Concordant localization	173(81.60%)	1 (0.58%)	172 (99.42%)	0.408	0.523
Discordant or negative localization	39(18.40%)	0 (0%)	39 (100%)		
Total	212	1 (0.47%)	211 (99.53%)		

TABLE 6 Relationship between parathyroid location and RLN injury.

	Number of examples	Persistent RLN signal abnormalities	Normal signal	χ^2	*P*
PHPT patients					
Superior parathyroid	63	2 (3.17%)	61 (96.83%)	0.184	0.668
Inferior parathyroid	222	3 (1.35%)	219 (98.65%)		
Total	285	5 (1.75%)	280 (98.25%)		
SHPT patients					
Superior parathyroid	106	1 (0.94%)	105 (99.06%)	1.391	0.499
Inferior parathyroid	99	0 (0%)	99 (100%)		
Ectopic parathyroid	7	0	7 (100%)		
Total	212	1 (0.47%)	211 (99.53%)		

3.7 Comparison of RLN injury between parathyroidectomy and thyroidectomy

Of the 323 patients who underwent parathyroidectomy with IONM, six (1.59%) RLN had transient RLN and no permanent injury. In comparison, twenty-three (5.32%) RLNs had a transient RLN injury and six (1.39%) RLNs had a permanent RLN injury in 432 RLNs in 300 patients who underwent thyroid lobectomy combined with lymph node dissection. The results showed that the likelihood of RLN injury was higher in patients who underwent radical thyroidectomy (P<0.001). See Table 10.

4 Discussion

IONM allows rapid localization of the nerve. Patients are characterized by morphological changes in the parathyroid gland, variable anatomical location, variations of the laryngeal nerve, and other features (19, 20). The incidence of the non-recurrent laryngeal nerve is statistically 0.26% to 0.99% on the right side and about 0.04% on the left side (21–24). 60.8% of the RLN runs within the tracheoesophageal groove, 4.9% of the RLN is more lateral to the trachea, and 28.3% of the RLN is directly posterior to the thyroid gland (25). The right RLN is more oblique in the paratracheal region than the left RLN (26); the RLN may be localized with the inferior thyroid artery in as many as 20 different ways (27, 28). Two non-recurrent laryngeal nerves have been identified at our center. Sometimes the arteriovenous thickness and morphology resemble the nerve, which is difficult to see with the naked eye; patients must undergo reoperation if the anatomy has changed, fibrous tissue is proliferating and there are severe tissue adhesions (5). All these conditions affect the accurate localization of the RLN, which in turn compromises the safety of the procedure. By using IONM to strictly implement the "four-step RLN monitoring method"," continuous intraoperative monitoring, and other technical nerve monitoring procedures (17, 29), the nerve can be quickly localized and differentiated, improving the protection of the nerve and shortening the localization time.

4.1 Analysis of the relationship between IONM and preoperative localization of parathyroid glands

Currently, ultrasonography (US), computed tomography (CT), and single-photon emission computed tomography (SPECT)-CT with sestamibi Tc99m can achieve 100% accuracy in the preoperative localization of parathyroid glands (2, 30). Therefore

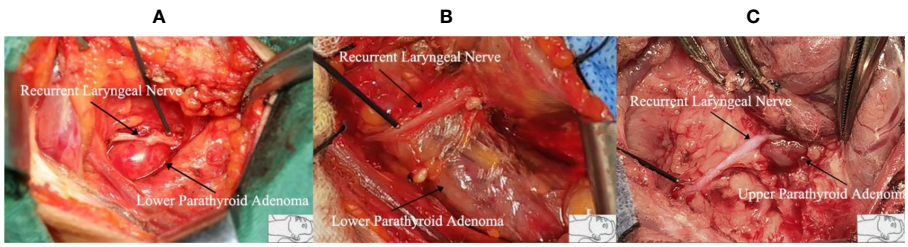

FIGURE 2
The different positions of the recurrent laryngeal nerve and parathyroid gland. **(A)** Inferior parathyroid adenoma protrudes upward. The recurrent laryngeal nerve is pushed up, and its course becomes shallow and easy to injure; **(B)** Inferior parathyroid adenoma is larger in size, grows toward the middle of the thyroid gland, and has a longer length of concomitant course with the recurrent laryngeal nerve, which makes the dissection of the recurrent laryngeal nerve more difficult; **(C)** Superior parathyroid adenoma is located at the point where the recurrent laryngeal nerve enters the larynx, where the surrounding tissues are dense. It is easy to injure and cause injury when the recurrent laryngeal nerve is separated from the mass.

TABLE 7 The relationship between parathyroid size and RLN injury.

	Number of examples	Persistent RLN signal abnormalities	Normal signal	χ^2	*P*
PHPT patients					
diameter ≥ 2cm	79	3 (3.80%)	76 (96.20%)	1.261	0.261
diameter <2cm	206	2 (0.97%)	204 (99.03%)		
Total	285	5 (1.75%)	280 (98.25%)		
SHPT patients					
diameter ≥ 2cm	71	1 (1.40%)	70 (98.59%)	2.197	0.138
diameter <2cm	141	0 (0.00%)	141 (100%)		
Total	212	1 (0.47%)	211 (99.53%)		

intraoperative exploration of parathyroid glands that are not localized is common. According to the data in this study, there was no relationship between the preoperative accuracy of parathyroid gland localization and RLN injury in PHPT patients and SHPT patients under IONM. This suggests that IONM also plays a role in laryngeal recurrent nerve protection in the exploration and removal of parathyroid glands that fail to be accurately localized. The study by Karakas E et al. (31) also confirms that IONM in combination with other techniques can be effective in protecting the RLN during PHPT surgery.

4.1.1 Analysis of the relationship between IONM and parathyroid gland location

The literature reports that the upper parathyroid gland is mainly located within 2 cm of the junction of the inferior thyroid artery and the RLN in the cricothyroid joint area (4), which is a risk area for RLN injury during upper parathyroid resection. The lower parathyroid gland is mainly located in the lower pole of the thyroid gland, usually on the lateral side of the RLN. Some ectopic parathyroid glands even continue into the anterior mediastinum; in some SHPT patients, a partial thymectomy is required for surgery (32). The above area has a long RLN pathway and is difficult to detect, and it is also a vulnerable area for RLN injury in PTX. In our study, there was no statistically significant effect of parathyroid location on RLN injury, suggesting that the neurological safety of PTX in PHPT and SHPT patients was significantly improved by the use of IONM. The study by Brian R et al. (33) is identical to the present study.

4.2 Analysis of the relationship between IONM and parathyroid gland size

Nowadays, more and more surgeons choose to perform resection of the diseased parathyroid gland with a monopolar or bipolar electrometer (34), which has the advantages of less bleeding, faster clotting, and a gentle procedure, but also increases the risk of mild nerve damage such as heat conduction. According to a study by Zhao et al. (35), the distance between the electric knife and the nerve is unsafe within 3 mm. In the present study, it was found that some normal-sized or hyperplastic parathyroid glands may have a smaller distance to the recurrent laryngeal nerve, up to 1.5 mm. In the present study, there was no statistically significant effect of parathyroid gland size on RLN injury, suggesting that the neurological safety of PTX is significantly improved with IONM in PHPT and SHPT patients. One study shared the results of the present study, in which the right upper parathyroid mass was up to 0.25 ± 0.39 cm closer to the RLN compared to other parathyroid glands, and there was no permanent RLN injury after surgery in 136 patients with IONM (33).

TABLE 8 The relationship between cure rate and RLN injury.

	Number of examples	Persistent RLN signal abnormalities	Normal signal	χ^2	*P*
PHPT patients					
Number of cures	269	5 (1.86%)	264 (98.14%)	0.008	0.931
Number of recurrences	1	0 (0.00%)	204 (100%)		
Total	270	5 (1.85%)	269 (99.63%)		
SHPT patients					
Number of cures	49	1 (2.04%)	48 (97.96%)	0.159	0.924
Number of persistent	1	0 (0.00%)	1 (100%)		
Number of recurrences	3	0 (0.00%)	3(100%)		
Total	53	1 (1.89%)	52 (98.11%)		

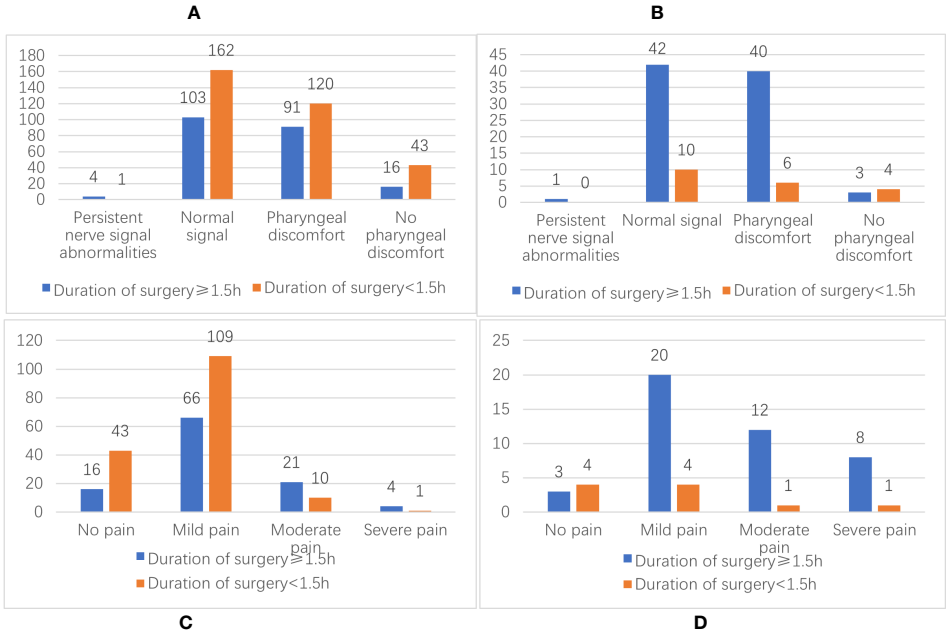

FIGURE 3
(A) Distribution of the duration of surgery and the number of RLN injuries and pharyngeal discomfort in PHPT patients; **(B)** Distribution of the duration of surgery and the number of RLN injuries and pharyngeal discomfort in SHPT patients; **(C)** Distribution of the number of PHPT patients with postoperative pharyngeal discomfort; **(D)** Distribution of the number of SHPT patients with postoperative pharyngeal discomfort.

IONM enables analysis of the mechanisms of nerve injury, prevention of nerve injury, and appropriate protection of nerves. With IONM, fifteen (5.51%) RLNs and five (4.76%) RLNs had abnormal intraoperative nerve signals in PHPT patients and SHPT patients in this study, and only five (1.84%) RLNs and one (0.95%) RLN, respectively, had abnormal nerve signals at the end of surgery. This is due to the continuous monitoring by the IONM, which provides real-time nerve signals to the surgeon. Any factors affecting the RLN signal are displayed and the surgeon can detect and avoid them in time through the IONM, which really protects the RLN. In an SHPT patient with a 2.1 x 0.9 cm left parathyroid gland, the RLN electromyographic signal R decreased from 1,226 V to 135 V when the parathyroid gland was exposed by pulling the thyroid gland during resection of the left upper parathyroid gland. The signal was restored by exposing the thyroid gland, indicating that the ligaments Berry was stuck in the left RLN, and the RLN signal was normal at the end of surgery. Three hundred and seventy-seven RLNs were identified in this group and dissected using IONM. The rate of transient injury in this group was 1.59%, with no permanent injury, and the rate of RLN injury was much lower than in PHPT patients without IONM (5.50%). It is also much lower than previous reports (6, 9, 36), which fully demonstrates the function of IONM in revealing and analyzing the mechanism of RLN injury and protecting the nerves.

Compared to parathyroidectomy, thyroid surgery poses a greater challenge to the protection of the RLN. In addition to the RLN anatomical factors described above, the infiltration of nerves by thyroid cancer, the greater length of the naked RLN, the presence of perioperative complications, the management of Berry's ligament, the high likelihood of bleeding and difficulty of

TABLE 9 Distribution of the number of RLNs with intraoperative signal abnormalities. .

	Persistent RLN signal abnormalities	Normal signal	Total number of RLNs	χ^2	*P*
PHPT patients					
Transient RLN signal abnormalities	5 (33.33%)	10 (66.77%)	15	30.776	<0.001
Normal signal	0 (0.00%)	257 (100.00%)	257		
Total	5 (1.84%)	265 (97.43%)	272		
SHPT patients					
Transient RLN signal abnormalities	1 (20.00%)	4 (80.00%)	5	6.294	0.012
Normal signal	0 (0.00%)	100 (100.00%)	100		
Total	1 (0.95%)	104 (99.05%)	105		

TABLE 10 RLN injury under different conditions.

Grouping	Normal RLN	RLN temporary injury	RLN permanent injury	Total number of RLNs	χ^2	*P*
Intraoperative PHPT patient with IONM	267 (98.16%)	5(1.84%)	0 (0.00%)	272	6.148	0.013
Intraoperative PHPT patient without IONM	102 (93.58%)	6 (5.50%)	1(0.92%)	109		
Patients with hyperparathyroidism	371 (98.41%)	6 (1.59%)	0 (0.00%)	377	13.539	<0.001
Patients with Thyroid cancer	403 (93.29%)	23(5.32%)	6 (1.39%)	432		

hemostasis near the RLN, lymph node dissection of the central group and multiple surgeries may affect the RLN signal (37–39). Therefore, thyroid surgery has a higher probability of RLN injury than parathyroid surgery, with the same statistical results as in the present study, with a probability of transient RLN injury of 5.32% and 1.59%, respectively. The rate of RLN injury in patients with thyroid cancer after IONM currently ranges from 2.6% to 6.0% (9, 14, 40).

Several studies have shown that IONM reduces the time to intraoperative detection of RLN by the surgeon (41, 42). In this study, we found that the duration of the procedure was not related to RLN injury and was associated with patients' postoperative pharyngeal discomfort. The duration of surgery has a direct correlation with the incidence of postoperative pharyngeal discomfort, with longer surgeries resulting in a higher likelihood of patients experiencing this discomfort. Additionally, those who do experience postoperative pharyngeal discomfort are more likely to report moderate to severe pain. Therefore, IONM might play a role in patients' postoperative pharyngeal pain. In this study, all patients underwent postoperative nebulization and oral inclusions and were discharged with significant symptom relief.

4.2.1 Protection of other nerves by IONM

Patients with damage to the outer branch of the SLN tend to have decreased pitch (43). There are several anatomical variants between the outer branch of the SLN and the superior(STA) thyroid artery, and there are many ways of typing. The accepted international typing standard is the Cernea (44). The outer branch of the SLN may pass below the upper margin of the superior thyroid pole and cross the STA, which is known as Cernea 2B, with an incidence of about 5% to 48.3% (45–47), in which the outer branch of the SLN passes in close relation to the superior parathyroid gland. Treatment of an abnormally enlarged upper parathyroid gland in patients with SHPT and PHPT can lead to nerve injury if not performed correctly. Cernea 2B SLN accounted for 25.39% (82/323) of cases in this group. IONM was used to monitor the continuity of the SLN throughout the procedure without injury. As there is currently no method to study SLN injury, only the patient's complaints of choking on water or change in tone were used and no complications occurred. Very few enlarged parathyroid glands in SHPT patients are ectopic near the cervical sheath in the lateral neck, and there is a risk of vagus nerve boot injury with PTX. The relationship between the vagus nerve, the carotid artery, and the internal jugular vein in the cervical sheath is variable (48, 49), so intraoperative attention must be paid to ectopic parathyroid glands and the course of the nerve carefully determined. Intraoperative IONM improves the identification of the vagus nerve and reduces identification time (50, 51). In our group of SHPT patients, two patients had two parathyroid glands in the unilateral cervical sheath, and one of the preoperative patients had a parathyroid gland near the vagus nerve, which could be removed without injury to the vagus nerve by using IONM.

This study has the following limitations: it is a single-center retrospective study, which may introduce selection bias and cannot exclude the effect of single-center. The sample size of patients with SHPT (53 cases) is relatively small, and all of them received IONM. Data from patients with SHPT who did not receive IONM were not obtained, nor were clinical data from thyroid cancer patients who did not use IONM collected. Therefore, no analysis was performed on the data of patients with SHPT and thyroid cancer, whether they used or did not use IONM, to investigate the protective effect of IONM on the recurrent laryngeal nerve during surgery for SHPT and thyroid cancer. In the future, large-sample, multi-center, and prospective studies with random sampling are needed to better understand the role of IONM in the surgical treatment of SHPT and thyroid cancer, and to obtain more definitive research conclusions.

5 Conclusion

In this retrospective study, it was found that the use of IONM in PTX of PHPT and SHPT patients can rapidly identify and localize the laryngeal nerve intraoperatively, determine the functional integrity of the nerve by electromyographic signals, analyze the mechanism of nerve injury, and reduce the risk of laryngeal nerve injury due to irregular parathyroid hyperplasia, anatomical abnormalities of the laryngeal nerve, and tissue adhesions. IONM is undoubtedly a better tool in PTX of SHPT and PHPT patients. More clinicians and patients will benefit from the comprehensive and accurate application of IONM in PTX.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part are appropriately investigated and resolved. The study was conducted by the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of China-Japan Union Hospital of Jilin University (approval number: 20230630016). The patients or their legal guardians sign a detailed informed consent form before surgery.

Author contributions

YM: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. XB: Writing – original draft, Writing – review & editing. JY: Data curation, Formal Analysis, Validation, Visualization, Writing – original draft. YL: Writing – review & editing. YuZ: Writing – review & editing. GD: Writing – review & editing. YiZ: Funding acquisition, Methodology, Supervision, Writing – review & editing. HS: Funding acquisition, Investigation, Methodology, Resources, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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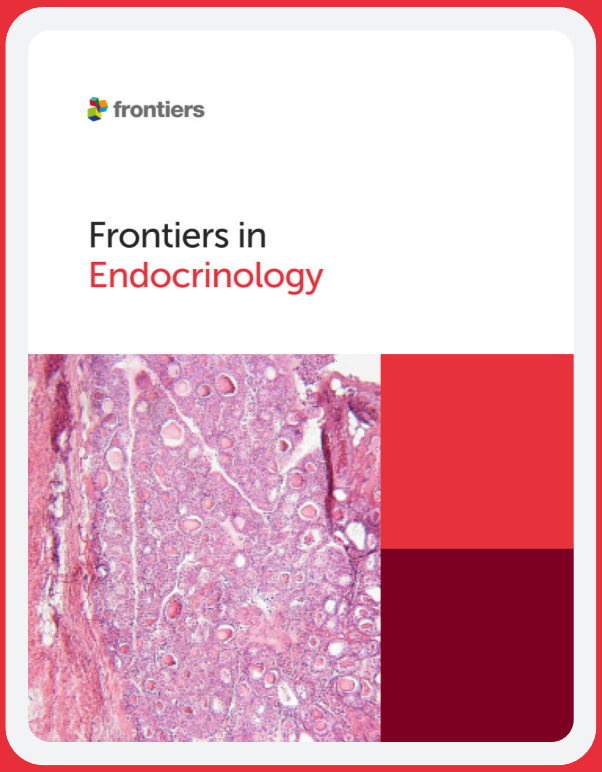

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