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ORIGINAL ARTICLE

The Patterns of Persistence and Recurrence Following Parathyroidectomy for Renal Hyperparathyroidism: A 10-year Review

Si-Yuan Wu[1], Yu-Cheng Chiu[1], Shun-Neng Hsu[2], Fu-Chiu Yu[2], Shih-Hua Lin[2], Ming-Lang Shih[1]

[1]Division of General Surgery, Department of Surgery, Tri-Service General Hospital, National Defence Medical Center, [2]Division of Nephrology, Department of Medicine, Tri-Service General Hospital, National Defence Medical Center, Taipei, Taiwan

Background: Renal hyperparathyroidism can be effectively treated with parathyroidectomy. However, managing persistence or recurrence after the initial surgery is still challenging. Understanding the anatomical patterns observed in reoperative parathyroidectomies can help localize the disease during initial and subsequent surgeries. **Aim:** This study aimed to identify the patterns of persistence and recurrence following parathyroidectomy for renal hyperparathyroidism and assess the performance of various localization studies. **Methods:** A retrospective cohort study was conducted on dialysis patients who underwent reoperative parathyroidectomy at a single center. Patient demographics, laboratory test results, localization study findings, surgical details, and postoperative outcomes were obtained through the chart reviews. Persistence was defined as an intact parathyroid hormone level >300 pg/mL within 6 months after the primary surgery; otherwise, recurrence was defined as > 6 months. **Results:** Among 377 patients who underwent parathyroidectomies, 20 (5.3%) required reoperations. Supernumerary glands were the primary cause of persistence (70%) and recurrence (50%), predominantly located posteriorly within the tracheoesophageal groove. Besides, overgrowth of the forearm graft accounted for 30% of recurrences. Neck ultrasound (US) showed 6 out of 19 false negatives (68% sensitivity and 100% specificity), whereas ^{99m}Tc-sestamibi scintigraphy with single-photon emission computed tomography (SPECT)/computed tomography (CT) had one false negative (95% sensitivity and 100% specificity). CT scans accurately localized the disease in cases where US and sestamibi scintigraphy yielded discordant results. **Conclusion:** Supernumerary glands frequently contribute to the persistence and recurrence of renal hyperparathyroidism after parathyroidectomy. In the reoperative context, sestamibi SPECT/CT and CT scans detect affected parathyroid tissue in the neck and mediastinum more effectively than neck USs.

Key words: Parathyroidectomy, hyperparathyroidism, chronic kidney disease, recurrence, persistence

INTRODUCTION

Renal hyperparathyroidism commonly occurs in long-term dialysis patients, accompanied by a metabolic imbalance that includes reduced phosphate clearance and the shortage of active Vitamin D. Conventionally, medical therapy involving restrictions of phosphate intake, Vitamin D, phosphate binders, or calcimimetics is used to manage this condition. However, parathyroidectomy becomes necessary in medically refractory cases. Parathyroidectomy also helps mitigate bone diseases and alleviate symptoms such as fatigue, muscle weakness, and joint pain. Total parathyroidectomy with autotransplantation and subtotal parathyroidectomy are acceptable procedures for renal hyperparathyroidism. Due to the scarcity of kidney donors in Taiwan, surgeons prefer total parathyroidectomy to minimize the risk of recurrence. Despite these efforts, approximately 5%–30% of patients require reoperation due to the persistence or recurrence of the disease.[1] Re-do parathyroid surgery carries a higher risk of bleeding and injury to the recurrent laryngeal nerve due to scarring, particularly

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Corresponding Author: Dr. Ming-Lang Shih, Division of General Surgery, Department of Surgery, Tri-Service General Hospital, National Defence Medical Center, No. 325, Sec. 2, Chenggong Rd., Neihu Dist., Taipei 114, Taiwan. Tel: +886-2-8792-7191; Fax: +886-2-8792-7372. E-mail: judeshih@gmail.com

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in uremic patients. Furthermore, accurately locating affected glands can be challenging when autografts are present in the forearm. Understanding the persistence/recurrence patterns following parathyroidectomy for renal hyperparathyroidism can assist surgeons in avoiding residual parathyroid tissue and interpreting localization test results accurately while dealing with recurrent diseases. However, existing observational studies provide inconsistent, insufficient, and conflicting data. Therefore, our objective is to identify the patterns of persistence/recurrence following a presumed total parathyroidectomy for renal hyperparathyroidism and assess the efficacy of various localization studies in the reoperative setting.

MATERIALS AND METHODS

We conducted a single-center, retrospective cohort study that included dialysis patients who underwent reoperative parathyroidectomy for renal hyperparathyroidism from January 2010 to December 2020. The clinical data were gathered from the chart reviews after receiving approval from the institutional review board (TSGH IRB No. 2-105-05-108). The patient consent was waived by the IRB.

At the hospital, the nephrologist diagnosed and managed renal hyperparathyroidism in dialysis patients. Patients were referred for parathyroidectomy when medical therapies, including diet modification, calcium and Vitamin D analog supplementation, and/or calcimimetics, could not control the disease. The common indications were refractory intact parathyroid hormone (PTH) >800 ng/dL over 6 months and/or osteodystrophy, joint pain, muscle weakness, calciphylaxis, and extensive soft-tissue calcification. Patients were evaluated for perioperative cardiac risks and performance status and suggested medical treatment alone if the estimated risks were too high. The preoperative localization tests for surgical candidates included neck ultrasound (US) and ^{99m}Tc-sestamibi scintigraphy with single-photon emission computed tomography (SPECT)/computed tomography (CT) scans (MIBI scans). CT scans were examined if MIBI scans revealed possible ectopic glands. In the primary operation, the total parathyroidectomy with forearm autotransplantation was performed if all four glands were identified. In the reoperative surgery, the Casanova test was selectively used to determine the recurrence source if the patient had forearm autograft in the primary operation. A positive Casanova test would be considered in case of; (1) over 50% drop of systemic PTH after 10 min of grafted arm ischemia; (2) 20%–50% drop of systemic PTH after 10 min of grafted arm ischemia and avid sestamibi uptake on forearm graft.

The cohort was identified by reviewing dialysis patients who had undergone more than one parathyroidectomy (including graft parathyroidectomy) during the study period. The following information was reviewed: age, sex, serial laboratory tests during the study period (PTH, calcium, and phosphate), the result of localization studies before each procedure, procedure details (date, times, and extent), removed glands details (anatomical location and pathology), postoperative events (complications and hunger bone syndrome), time to recurrence, and last follow-up time.

During the study period, total parathyroidectomy with forearm autotransplantation was the procedure of choice if all four glands were identified and showed asymmetric enlargement. Subtotal parathyroidectomy was done if the surgeon could not confidently identify all the four glands.

The persistent disease was defined by PTH >300 pg/mL within 6 months of surgery. At the same time, the recurrent disease was defined by recurrent hyperparathyroidism (PTH >300 pg/mL not responding to medical treatment) after more than 6 months of surgery. The reason for the persistence or recurrence for each patient was determined by the last procedure that successfully controlled PTH <300 pg/mL or the last localization test, clearly showing the parathyroid gland. The supernumerary gland was considered when more than four glands were required to be removed to reach a biochemical cure. Missed gland in the primary surgery was considered if patients developed persistence or recurrence and three or fewer glands were identified in the primary surgery. The anatomical locations of the parathyroid gland were categorized using a standard nomenclature system proposed by Perrier *et al*. 2009.[2] Type A parathyroid glands adhere to the posterior thyroid parenchyma, located explicitly behind the upper pole of the thyroid gland but not entirely within the thyroid tissue. Type B parathyroid glands are posterior to the thyroid parenchyma within the tracheoesophageal groove. The B + subcategory encompasses adenomas in retroesophageal, high lateral pharyngeal, and carotid sheath regions. Type C parathyroid glands are situated caudal (inferior) to the thyroid parenchyma within the tracheoesophageal groove. They are positioned lower than type B glands when viewed laterally and can be found beneath the inferior thyroid pole, closer to the clavicle. Type D parathyroid glands are located directly over the recurrent laryngeal nerve at the level of the inferior thyroid vessels. Type E parathyroid glands are situated in the external aspect of the inferior thyroid pole. They are positioned more superficially in the anterior–posterior plane than type D. Type F parathyroid glands are characterized by their displacement into the thyrothymic ligament below the inferior pole of the thyroid in a pretracheal plane. Type G parathyroid glands are intrathyroidal and considered "gauche."

RESULTS

From 2010 to 2020, 377 patients underwent parathyroidectomy for renal hyperparathyroidism at our institution. Out of these patients, 324 primary operations involved total parathyroidectomy. Further, 20 (5.3%) required more than one parathyroidectomy, with 10 cases due to persistence and 10 cases due to recurrence. The occurrence of persistence was higher in subtotal parathyroidectomy compared to total parathyroidectomy [5.7% vs. 2.2%, as depicted in Figure 1]. All three persistence cases following subtotal parathyroidectomy were owing to the missed glands in the primary surgery.

Neck exploration was the most commonly performed procedure in reoperative parathyroidectomy, carried out 18 times in 16 patients. Five patients underwent reoperation twice, including four cases of neck exploration following graft parathyroidectomy [Table 1, patients 1 and 5–7] and one repeat neck exploration. Graft parathyroidectomy was performed in 8 instances involving seven patients. In contrast, three patients required another procedure to remove parathyroid tissue in the neck or mediastinum to achieve a cure [Table 1, patients 5–7]. Two patients underwent video-assisted thoracoscopic surgery to remove mediastinal parathyroid tissue.

Persistence (7 of 10, 70%) and recurrence (5 of 10, 50%) of the disease were primarily caused by supernumerary glands [Table 2]. Anatomically, 58% of the glands were located posteriorly (5 type B, 3 type B+, and 3 type C), while 26% were situated in the anterior mediastinum through the thyrothymic ligament (type F). In persistent disease resulting from missed glands during the primary surgery, two glands were located in type B+ [as shown in Figure 2] and one in type G. Recurrent disease was attributed to the overgrowth of forearm graft as the second most common cause (30%), followed by missed glands during the primary surgery (20%).

Table 3 illustrates the performance of various diagnostic tests in the reoperative setting. Neck US produced 6 false negatives out of 19 tests, with a 68% of sensitivity and 100% of specificity for detecting persistent or recurrent disease. MIBI scans exhibited 95% sensitivity and 100% specificity. CT scans accurately detected the persistent or recurrent disease in all cases, even in 5 instances where previous results from US and MIBI scans were inconsistent (negative US and positive MIBI scans).

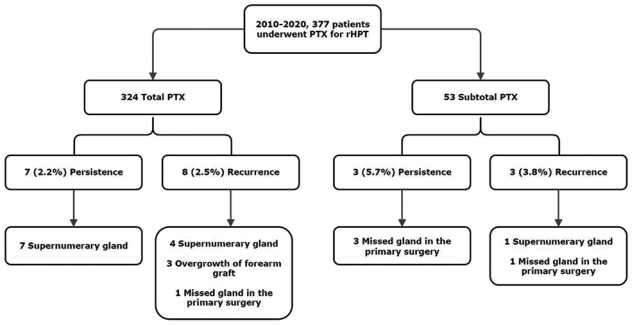

Figure 1: The reasons for persistence and recurrence by procedures. PTX: = parathyroidectomy, rHPT = renal hyperparathyroidism

DISCUSSION

The supernumerary gland is the main cause of disease persistence and recurrence after presumed total parathyroidectomy in renal hyperparathyroidism patients. The remaining parathyroid tissue, typically located in the neck, presents complexities in terms of anatomical positions such as type B and F. If functional parathyroid tissue remains in the neck, performing graft parathyroidectomy alone does not significantly lower the PTH levels (<300 pg/mL) regardless the outcome of the Casanova test. These findings highlight the importance of preoperative localization studies in reoperative scenarios. Compared to neck US, MIBI scans with SPECT and CT scans offer greater sensitivity as diagnostic tests.

Supernumerary parathyroid glands are additional parathyroid glands to the usual four, which existed in 13% of the cases in an autopsy study by Akerström *et al*.[3] The reported incidence is up to 30% in renal hyperparathyroidism patients.[4-6] In a meta-analysis including 501 patients from 53 papers, supernumerary glands were identified in 7% of patients during the primary operation and accounted for 29% of persistent or recurrent disease at reoperations.[6]

In the current study, supernumerary glands account for 7 of 10 persistent diseases. These findings align with a retrospective study that included 1156 uremic patients with

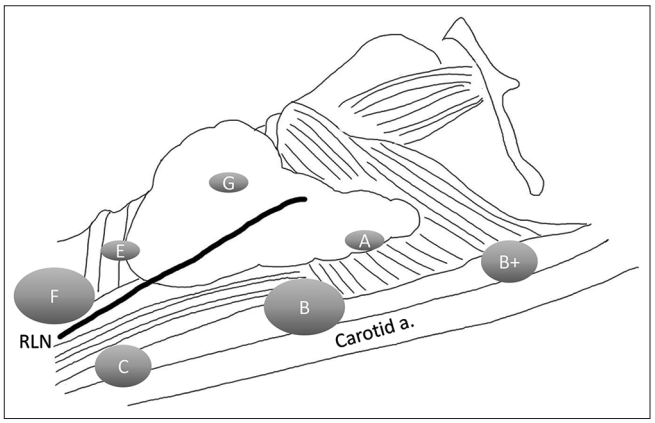

Figure 2: The anatomical location of parathyroid glands for persistent and recurrent diseases. The alphabet stands for each type in Perrier's classification and the size of glands stands for its relative incidence [refer to Table 2]. RLN = recurrent laryngeal nerve

Table 1: The parathyroid hormone changes after graft parathyroidectomies versus various localization test

Patient	Procedure (by orders)			Findings of localization tests before reoperation	
	1	2	3	Casanova test (%)	MIBI scans
Patients cured after graft parathyroidectomies					
1	1311 ⟫ 17.5	2500 ⌦ 138	2500 ⌦ 3.7		Forearm
2	1300 ⟫ 226	1001 ⌦ 176		Positive (77)	
Patients not cured after graft parathyroidectomies					
3	1305 ⟫ 308	1800 ⌦ 1688		Positive (61)	Neck
4	1688 ⟫ 21.2	610 ⌦ 387			Forearm
Patients cured by re-exploration of neck or mediastinum after graft parathyroidectomies					
5	1079 ⟫ 22	828 ⌦ 353	954 @ 56.9	Positive (69)	Neck
6	998 ⟫ 200	1996 ⌦ 771	771 @ 35.2		Neck and forearm
7	676 ⟫ 14.5	1218 ⌦ 396	1252 # 27.8	Positive (75)	Mediastinum

Procedure codes=⟫ total parathyroidectomy; ⌦ removal of forearm graft; @ neck re-exploration; # mediastinum re-exploration. MIBI=^{99m}Tc-sestamibi scintigraphy with single-photon emission computed tomography

Table 2: Reason for persistence or recurrence by the anatomical location

	Persistence (*n*=10)		Recurrence (*n*=10)			Subtotal, *n* (%)
	Supernumerary gland (*n*=7)	Missed gland in the primary surgery (*n*=3)	Supernumerary gland (*n*=5)	Missed gland in the primary surgery (*n*=2)	Overgrowth of forearm graft (*n*=3)	
Type A			1*			1 (5)
Type B	2		2	1		5 (26)
Type B+	1	2				3 (16)
Type C	2			1		3 (16)
Type D						
Type E			1*			1 (5)
Type F	2		3*			5 (26)
Type G		1				1 (5)

*One patient had three glands (type A, B, and F) removed in two procedures

Table 3: Performance of ultrasound, MIBI scans, and computed tomography scans for reoperative parathyroidectomies

	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)
US	13	1	-	6	68	100
MIBI scans	21	2	-	1	95	100
CT scans	11	-	-	-	100	-

TP=True positive; TN=True negative; FP=False positive; FN=False negative; CT=Computed tomography; US=Ultrasound; MIBI=^{99m}Tc-sestamibi scintigraphy with single-photon emission computed tomography

total parathyroidectomy, where 7 out of 9 patients with last PTH >500 pg/mL were due to the supernumerary gland.[7]

Supernumerary glands could be found in usual or ectopic locations. In the current study, these glands were most commonly located in the mediastinum along the thyrothymic ligament (type F) or behind the thyroid parenchyma (type B or B+), which was in line with the literature.[5,8-10] A few studies advocate routine transcervical thymectomy and carotid sheath exploration to remove all the parathyroid tissue during bilateral neck exploration for renal hyperparathyroidism.[6,7,10,11] However, a negative exploration could complicate reoperations in future. The supernumerary glands found during recurrences could be too small to be identified during the primary surgery since the pathogenesis of renal hyperparathyroidism continues in patients without renal transplantation. In our practice, we do not routinely remove the thymus or explore the carotid sheath unless evident ectopic glands on preoperative localization tests or less than two glands are identified during unilateral exploration. The optimal extent of exploration could be better defined with intraoperative PTH monitoring, which has been shown to help reduce the rate of persistent and recurrent disease.[12] However, the optimal criteria for success are yet to be defined in terms of the third-generation PTH assay, a more specific assay for uremic patients.[1]

Total parathyroidectomy with forearm autograft is the preferred procedure in our practice since recurrence from autograft could be safely removed compared to reoperative neck

exploration. When dealing with recurrent disease, the critical issue is its localization, which could be at the forearm, neck, or ectopic locations. Few studies reported the management of recurrence following total parathyroidectomy.[7,13-15] Chou *et al*. reported that 10 of 11 recurrences were from the forearm graft, in which the PTH gradient (blood drawing from the graft-bearing arm versus the contralateral arm) was >2.[13] Tominaga *et al*. showed that 248 of 2660 (9.3%) patients required forearm graft removal during long-term follow-up. Among them, 87.1% were controlled by graft parathyroidectomy, and 12.9% still required resection of the residual parathyroid gland in the neck or mediastinum.[15] The graft-dependent recurrence was determined by a PTH gradient of 1.5 and/or a positive Casanova test. In the current study, 7 of 10 patients with recurrence underwent graft parathyroidectomy; however, the procedure reduced PTH to below 300 pg/mL in only two patients and three patients still required another operation to resect recurrent disease in the neck or mediastinum [Table 1]. Notably, these three patients had positive MIBI scans in the neck or mediastinum. Therefore, we suggest prioritizing MIBI and/or CT scans for recurrent diseases. Casanova test or PTH gradient could help detect hyperfunctioning autograft but should be interpreted with a negative MIBI/CT scan result outside the forearm.

Localization tests for renal hyperparathyroidism are challenging due to the diffuse and multifocal nature of parathyroid hyperplasia associated with chronic kidney disease. US is the initial screening tool for renal hyperparathyroidism detection. It provides the surgeon with an anatomical map for preoperative planning without ionizing radiation, while it is less sensitive to renal hyperparathyroidism than primary hyperparathyroidism.[16] In the reoperative setting, the US performance may be further reduced due to poor visualization of the retroesophageal location and thymic tongue, common disease locations in the current study. The sestamibi parathyroid scans can also help localize abnormal parathyroid glands in renal hyperparathyroidism. However, their sensitivity may be lower compared to primary hyperparathyroidism due to the asymmetrical and multifocal nature of the hyperplasia. In a meta-analysis, ^{99m}Tc-sestamibi parathyroid scintigraphy showed inadequate diagnostic accuracy for secondary hyperparathyroidism, with 58% and 93% pooled sensitivity and specificity, respectively.[17] However, for parathyroid in the upper mediastinum and thymus, sestamibi scintigraphy scans performed better than the US (69.7% vs. 45.5%).[8] Moreover, the sensitivity of MIBI scans is generally higher (71%–95%) in the reoperative setting.[13,18-21] Parathyroid scintigraphy is frequently performed with SPECT/CT, which is superior to SPECT and scintigraphy in detecting ectopic glands.[22] These findings explain the high sensitivity (95%) of MIBI scans in the current study, where SPECT/CT is routinely included in MIBI scans.

The multiphasic dynamic contrast-enhanced CT scan provides significant value in situations with conflicting or inconclusive results from the ^{99m}Tc-sestamibi and US examination. In particular, it is proven to be beneficial in cases of unsuccessful initial surgery or when dealing with distorted neck anatomy.[23] This imaging technique delivers clear and detailed images to surgeons, illustrating anatomical relationships and the presence of feeding vessels, which play a vital role in preoperative planning. While CT scans may not be as accurate in identifying multigland disease in primary hyperparathyroidism, it remains a valuable tool for locating ectopic glands that are difficult to detect using neck US, such as those in the mediastinum, thymus, tracheoesophageal groove, and retrosternal space.[4,13] As observed in the current study and other reports, these locations are frequently associated with supernumerary or missing glands in reoperations. Therefore, based on these findings, a CT scan is an excellent complementary tool to MIBI scans in reoperative parathyroidectomy for renal hyperparathyroidism.

The study's limitations primarily stem from biases associated with its retrospective design, particularly the selection bias. The study only includes patients who underwent surgery after a positive localization test, potentially overlooking patients with all negative localization tests. This selection bias could lead to overestimating the sensitivity of the localization tests in the study. In addition, the true incidence of recurrent disease might be underestimated due to the high risk associated with reoperative surgery, which some patients may need help to avoid. However, despite these selection biases, persistent and recurrent disease patterns are unlikely to change. These findings provide surgeons with valuable knowledge when managing patients who require reoperative parathyroidectomy.

CONCLUSION

The most common cause of persistence and recurrence after parathyroidectomy for renal hyperparathyroidism is the supernumerary gland, which is frequently located in the neck. CT and MIBI scans are the more sensitive localization studies for the complex anatomies, specifically posterior to the thyroid or in the mediastinum in the reoperative setting. The interpretation of a Casanova test might be more accurate with negative MIBI scans and CT scans in the neck and mediastinum. These findings provide valuable insights for surgeons to avoid leaving parathyroid tissue behind and accurately interpret localization tests when dealing with persistent/recurrent disease.

Data availability statement

The data that support the findings of this study are available from the corresponding author, ML Shih, upon reasonable request.

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Conflicts of interest
There are no conflicts of interest.

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