Original Article

Changes in the pathophysiology of primary hyperparathyroidism and analysis of postoperative recurrence cases at a regional core hospital in Japan: experience of 35 years in Shinshu University Hospital

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Background: Since reoperation for recurrent primary hyperparathyroidism (PHPT) increases the risk of complications, such as recurrent laryngeal nerve palsy, it is vital to prevent recurrence as much as possible when performing the initial surgery. Therefore, we retrospectively analyzed the PHPT cases at Shinshu University Hospital from 1986 to 2020 for changes in the characteristics of PHPT over time and features of the recurrent cases to establish treatment strategies to prevent a postoperative recurrence.

Methods: Hereditary PHPT was diagnosed through endocrinological tests, systemic imaging, and/or genetic testing. Localization of swollen parathyroid glands was identified through neck ultrasonography (US), contrast-enhanced computed tomography, magnetic resonance imaging (MRI), and ^{99m}Tc-sestamibi scintigraphy.

Results: Among the 536 patients with PHPT (374 women and 162 men) with a mean age of 56.9±13.6 years, 90 (16.8%) had hereditary PHPT, while the other 446 (83.2%) had sporadic PHPT. Overall, 314 (58.6%) patients were asymptomatic, whereas 132 (24.6%) had symptoms related to PHPT. Asymptomatic PHPT was significantly more prevalent after 2001 (81.8%) than before 2001 (51.2%) ($P<0.01$), although the number of PHPT cases increased during the last decade. Resection of an enlarged parathyroid gland alone was performed for sporadic PHPT, while focused parathyroidectomy was performed after 2001. Total parathyroidectomy (TPTx) with autotransplantation was performed in patients with hereditary PHPT. In addition, the intraoperative rapid pathological diagnosis of the resected gland throughout the period and intraoperative serum intact parathyroid hormone (PTH) measurement from 2014 were used. Overall, 11 patients with hereditary PHPT (2.1%) developed recurrence. A recurrent parathyroid gland was identified in 10 of 11 cases through ^{99m}Tc-sestamibi scintigraphy.

Conclusions: Although the incidence of asymptomatic PHPT has been increasing recently, focused parathyroidectomy is considered an appropriate procedure for sporadic PHPT that has been carefully examined preoperatively. Therefore, in the future, it will be necessary to conduct genetic testing for sporadic PHPT cases as much as possible to accurately diagnose the disease type and decide on a treatment strategy.

Keywords: Primary hyperparathyroidism (PHPT); recurrence; parathyroidectomy; multiple endocrine neoplasia type 1

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Introduction

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia. It is characterized by increased serum calcium levels due to excessive parathyroid hormone (PTH) production by one or more parathyroid glands, which gains inappropriate autonomy. The effects of excess PTH on the bones and kidneys result in abnormal calcium and phosphate levels in the blood, causing hypercalcemia (1-3). Symptoms include kidney stones, gastroesophageal reflux disease, peptic ulcers, and fragility fractures due to osteoporosis; however, most patients do not exhibit typical symptoms and may complain of non-specific symptoms such as weakness, fatigue, joint pain, insomnia, and depression. Moreover, it has been linked to an increased risk of death from cardiovascular diseases (1,4). Recently, there has been an increase in the number of incidental PHPTs, which are asymptomatic and discovered when hypercalcemia is specified by medical examinations (5). Pathologically, among all patients, 75–80% had a single parathyroid adenoma, 15–20% had parathyroid hyperplasia, whereas parathyroid carcinoma was rare, accounting for <1% (6). Following the recent improvements in the performance of ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and the introduction of ^{99m}Tc-sestamibi scintigraphy, the accuracy of preoperative local diagnosis has improved (7-12). In many institutions, surgical resection is the first treatment choice for PHPT, and focused parathyroidectomy (FPTx) has become the main procedure when the preoperative diagnosis indicates a single enlarged gland. However, in the case of multiple endocrine neoplasias (MEN), it may sometimes be difficult to identify all glands both preoperatively and intraoperatively. Therefore, there may be a recurrence of PHPT due to residual glands. In addition, it is not rare for patients with MEN to have more than five parathyroid glands (13,14). Since reoperation for recurrent PHPT increases the risk of complications, such as recurrent laryngeal nerve palsy, it is vital to prevent recurrence as much as possible when performing the initial surgery.

In this study, we retrospectively reviewed the cases with PHPT who underwent surgery in our hospital during the last 35 years and analyzed the changes in the characteristics of patients with PHPT over time. Furthermore, to establish treatment strategies to prevent a postoperative recurrence of PHPT, we analyzed the characteristics of cases that required reoperation for PHPT recurrence. Subsequently, we discussed what should be considered during initial surgery to prevent a recurrence. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1171/rc).

Highlight box

Key findings

- Focused parathyroidectomy is considered an appropriate procedure for sporadic primary hyperparathyroidism that has been carefully examined preoperatively.

What is known and what is new?

- The incidence of asymptomatic primary hyperparathyroidism has increased in the United States and Europe.
- The incidence of asymptomatic primary hyperparathyroidism has been increasing in a local city in Japan. As for treatment, focused parathyroidectomy is considered an appropriate procedure for sporadic primary hyperparathyroidism that has been carefully examined preoperatively.

What is the implication, and what should change now?

- Although the frequency of postoperative recurrence of primary hyperparathyroidism with conventional treatment strategies is low, it will be necessary to conduct genetic testing for sporadic primary hyperparathyroidism cases as much as possible to prevent a postoperative recurrence.

Methods

Patients and study design

This was a retrospective cohort study. In this study, we retrospectively analyzed all patients diagnosed with PHPT indicated for surgery and referred to our department and operated at Shinshu University Hospital between 1986 and 2020. Most patients were referred to our department for surgery after being diagnosed with PHPT and were indicated for surgery by endocrinologists. We obtained the clinical data of 536 PHPT patients operated on at our hospital during this period from their clinical records. The clinical investigation ethics committee of Shinshu University approved this study (No. 4501). The requirement for informed consent was waived since this was a retrospective study of anonymized data. This study complied with the provisions of the Declaration of Helsinki (as revised in 2013). We publicized the study on the hospital's website and on postings in the hospital to ensure that the participants had the opportunity to opt out.

The following clinicopathological information was retrospectively collected from the patients' medical records: age, sex, serum calcium and intact PTH (i-PTH) levels, results of imaging diagnoses, surgical procedure, and histopathological findings of resected parathyroid glands.

Preoperative diagnosis

The diagnosis of PHPT was established by detecting (I) elevation of the serum calcium and i-PTH level over the normal limit (calcium, 8.7–10.2 mg/dL; i-PTH, 10.0–65.0 pg/mL), and (II) the presence of at least one swollen parathyroid gland through imaging modalities—neck US, contrast-enhanced CT, and ^{99m}Tc-sestamibi scintigraphy with single-photon emission computed tomography (SPECT). Contrast-enhanced MRI was performed if these three modalities did not detect the responsible gland. The responsible gland was determined when the swollen parathyroid glands were detected by at least two of these four modalities.

Endocrinological tests with blood and urine were performed by endocrinologists in our hospital in almost all patients, regardless of the presence or absence of a family history of the endocrine disease, to differentiate the possibility of MEN in patients with PHPT. For patients with a family history of PHPT or clinically suspected familial PHPT, systemic imaging was performed to rule out the presence of other endocrine neoplasms. Moreover, genetic testing was performed on patients who consented to the test. However, MEN type 1 (MEN1) was diagnosed without genetic testing in some patients with a strong family history of MEN1. None of the patients who underwent surgery for PHPT were subsequently diagnosed with MEN type 2A (MEN2A).

Surgical treatment

Removal of an enlarged gland was performed in patients with sporadic PHPT with a single responsible and swollen gland detected through preoperative diagnostic imaging and no clinical evidence of hereditary PHPT. Until 2000, the absence of swollen parathyroid glands other than the enlarged parathyroid gland detected through preoperative diagnostic imaging was confirmed by the intraoperative exploration of the bilateral parathyroid areas (i.e., bilateral neck exploration). Subsequently, the enlarged gland alone was removed. Since 2001, removal of the enlarged gland and visual confirmation on the same side alone (i.e., focused parathyroidectomy, FPTx) was performed.

Meanwhile, total parathyroidectomy (TPTx) with autotransplantation was performed in the following cases: (I) patients diagnosed as MEN1 or other hereditary PHPT, and (II) patients where multiple swollen glands were detected during the operation. When four parathyroid glands could not be identified, the paratracheal adipose tissue and bilateral superior poles of the thymus were excised. Subsequently, autotransplantation was performed as follows: after the resection of four parathyroids detected in operation, approximately 80 mg of parathyroid tissue excised from the most likely normal gland among the resected glands was cut into 12–15 pieces approximately 3 mm^3 in size; each parathyroid piece was transplanted into the brachioradialis muscle of the forearm in the non-dominant side.

The following three methods were used to facilitate the identification of the parathyroid gland during surgery: (I) intravenous administration of methylene blue (5 mg/kg) at the beginning of the operation; (II) intraoperative rapid pathological diagnosis of the resected gland; and (III) since 2014, intraoperative serum i-PTH measurement has been used to confirm whether or not the responsible parathyroid gland has been successfully removed when performing FPTx.

Postoperative follow-up

Serum calcium and i-PTH levels were monitored for at least 6 months postoperatively. PHPT recurrence was defined as hypercalcemia presenting after a normocalcemic interval for more than 6 months after the initial surgery (2).

Statistical analyses

Statistical analyses between the two and multiple groups were performed using the chi-square and Kruskal-Wallis tests, respectively. All statistical analyses were performed using the JMP (SAS Institute Japan, Tokyo, Japan). Statistical significance was set at $P<0.05$.

Results

Clinicopathological characteristics of patients and comparison between the sporadic and hereditary PHPT

Patient characteristics are presented in *Table 1*. Overall, 536 patients with a mean age of 56.9±13.6 years were analyzed in the study. Among them, 162 (30.2%) and 374

Table 1 Clinicopathological characteristics of patients

Characteristics	Total (n=536)	Sporadic (n=446)	Hereditary (n=90)	P value
Age (years), mean ± SD [range]	56.9±13.6 [13–87]	59.0±12.8 [20–87]	46.3±12.2 [13–73]	<0.01
Sex, n (%)				
Male	162 (30.2)	125 (28.0)	37 (40.7)	0.02
Female	374 (69.8)	321 (72.0)	53 (59.3)	
Type of PHPT, n (%)				
Sporadic	446 (83.2)	446 (100.0)	N/A	<0.01
Asymptomatic	314 (58.6)	314 (70.4)	N/A	
Bone fracture/osteoporosis	52 (9.5)	52 (11.7)	N/A	
Nephrolithiasis	80 (14.9)	80 (17.9)	N/A	
Hereditary	90 (16.8)	N/A	90 (100.0)	
MEN	87 (16.4)	N/A	87 (96.7)	
FIHP	2 (0.4)	N/A	2 (2.2)	
HPT-JT	1 (0.2)	N/A	1 (1.1)	
Surgical procedures, n (%)				
Unilateral neck exploration	310 (57.8)	297 (66.6)	13 (14.4)	<0.01
FPTx	251 (46.8)	248 (55.6)	3* (3.3)	
Resection of two parathyroid glands	59 (11.0)	49 (11.0)	10 (11.1)	
Bilateral neck exploration	226 (42.2)	149 (33.4)	77 (85.6)	
Resection of one parathyroid gland	127 (23.7)	124 (27.8)	3* (3.3)	
Resection of three parathyroid glands	20 (3.7)	10 (2.2)	10 (11.1)	
TPTx with autotransplantation	79 (14.7)	15 (3.4)	64 (71.1)	
Histopathological diagnosis, n (%)				
Adenoma	430 (80.2)	421 (94.4)	9 (10.0)	<0.01
Hyperplasia	103 (19.2)	24 (5.4)	79 (87.8)	
Carcinoma	3 (0.6)	1 (0.2)	2 (2.2)	
Recurrence, n (%)	11 (2.1)	0 (0.0)	11 (12.2)	<0.01

*, diagnosed as sporadic PHPT at the time of initial surgery. PHPT, primary hyperparathyroidism; MEN, multiple endocrine neoplasia; FIHP, familial isolated hyperparathyroidism; HPT-JT, hyperparathyroidism-jaw tumor syndrome; FPTx, focused parathyroidectomy; TPTx, total parathyroidectomy; N/A, not applicable.

(69.8%) were male and female (female-to-male ratio, 2.3:1), respectively. In addition, 90 patients (16.8%) were eventually diagnosed with hereditary PHPT, of which 87 cases had MEN1, two had familial isolated hyperparathyroidism (FIHP), and one had hyperparathyroidism-jaw tumor (HPT-JT) syndrome. The other 446 (83.2%) patients were diagnosed with sporadic PHPT. The mean age and proportion of female patients were significantly higher in the sporadic group (59.0±12.8 years and 72.0%, respectively) than in the hereditary group (46.3±12.2 years and 59.3%, respectively) (P<0.01 and P<0.05, respectively).

Overall, 314 (58.6%) patients had asymptomatic PHPT, whereas 132 (24.6%) patients had symptoms related to PHPT. Specifically, 52 (9.5%) and 80 (14.9%) patients had a history of bone fracture or osteoporosis and nephrolithiasis,

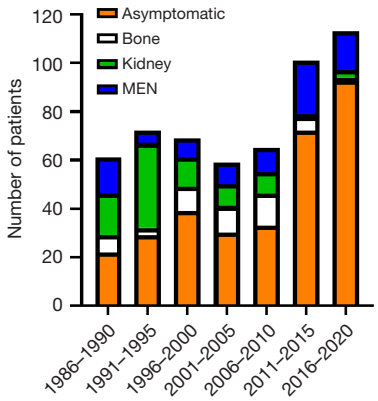

Figure 1 Changes in the types of primary hyperparathyroidism at Shinshu University Hospital over 35 years. The bar chart shows the type of hyperparathyroidism for every 5 years from 1986 to 2020. MEN, multiple endocrine neoplasia.

respectively.

Regarding the surgical procedure, unilateral and bilateral neck exploration were performed in 83.2% (446/536) and 16.8% (90/536) of overall PHPT cases, respectively. Furthermore, 66.6% (297/446) of patients with sporadic PHPT underwent unilateral neck exploration, 248 (55.6%) had FPTx, and 49 (11.0%) underwent resection of two parathyroid glands on one side. The unilateral neck exploration was performed significantly more frequently in the sporadic group than in the hereditary group (P<0.01). The bilateral neck exploration was performed in 33.4% (149/446) of sporadic PHPT cases. Moreover, 85.6% (77/90) of hereditary PHPT cases underwent bilateral neck exploration, of which TPTx with autotransplantation was performed in 64 patients. In 10 (11.1%) cases of hereditary PHPT, resection of three parathyroid glands and paratracheal adipose tissue with the bilateral superior poles of the thymus was performed since intensive exploration did not identify a fourth parathyroid gland. Six patients with hereditary PHPT underwent FPTx or resection of one parathyroid gland with bilateral neck exploration as they had been diagnosed with sporadic PHPT during surgery.

As for the histopathological diagnosis, 430 (80.2%), 103 (19.2%), and 3 (0.6%) cases were adenoma, hyperplasia, and carcinoma, respectively. Notably, no patients had multiple enlarged glands with a histopathologically different diagnosis. Adenoma was significantly more frequently observed in the sporadic group (94.4%) than in the hereditary group (10.0%) (P<0.01). Among the patients with hereditary PHPT, nine and two were diagnosed with adenoma and carcinoma, respectively.

Eleven (2.1%) patients developed recurrent PHPT. Although all recurrent cases were hereditary PHPT, FPTx was performed in three cases because they had been diagnosed as sporadic PHPT during the initial operation. The recurrence rate of hereditary PHPT was significantly higher than that of sporadic PHPT.

Changes in clinicopathological characteristics over time

Figure 1 shows the total number of patients with PHPT and the number of patients by symptoms every 5 years over the past 35 years. Approximately 60–70 cases were treated with surgery every 5 years from 1986 to 2010. However, the number of PHPT cases increased during the last decade, with 97 cases from 2011 to 2015 and 113 from 2016 to 2020. In addition to the increase in patients with PHPT, differences were observed in the causes of PHPT diagnosis before and after 2010. Before 2010, symptomatic sporadic PHPT (i.e., bone and renal type) accounted for approximately 30–50% of the PHPT cases. However, these types of PHPT became rare after 2010, accounting for only 6.9% from 2011 to 2015 and 3.5% from 2016 to 2020, and asymptomatic PHPT became dominant. Furthermore, hereditary PHPT increased after 2010, with 22 cases from 2011 to 2015 and 16 cases from 2016 to 2020, compared to 5–15 cases every 5 years before 2010.

As the alteration of PHPT type over the past 35 years was observed, the patients were categorized into two groups before and after the discontinuation of bilateral neck exploration for sporadic PHPT (i.e., 1986–2000 group and 2001–2020 group). In addition, clinicopathological features were also compared, including age, sex, surgical procedures, histopathological diagnosis, and recurrence of sporadic and hereditary PHPT (*Table 2*).

No significant difference was observed in the mean age (P=0.07) or sex distribution (P=0.16) for sporadic PHPT before and after 2001. Regarding the clinical type of PHPT, asymptomatic PHPT was significantly more prevalent in the 2001–2020 group (81.8%) than in the 1986–2000 group (51.2%) (P<0.01). Until 2000, an enlarged parathyroid gland was resected after confirming no other swollen gland in the bilateral peri-thyroid area for sporadic PHPT. Therefore, 74.7% of sporadic PHPT cases underwent resection of one parathyroid gland with bilateral neck exploration. Since the treatment strategy for sporadic PHPT was changed after 2001, 88.6% of patients had FPTx. Nine patients with sporadic PHPT underwent bilateral neck exploration during

Table 2 Comparison of the characteristics of clinicopathological findings in sporadic and hereditary PHPT before and after 2000

Characteristics	Sporadic PHPT			Hereditary PHPT		
	1986–2000 (n=166)	2001–2020 (n=280)	P value	1986–2000 (n=33)	2001–2020 (n=57)	P value
Age (years), mean ± SD [range]	57.4±13.0 [21–82]	60.0±12.6 [20–87]	0.02	48.6±11.2 [23–73]	44.6±12.4 [13–72]	0.06
Sex, n (%)						
Male	53 (31.9)	72 (25.7)	0.16	13 (39.4)	24 (42.1)	0.80
Female	113 (68.1)	208 (74.3)		20 (60.6)	33 (57.9)	
Type of PHPT, n (%)						
Asymptomatic	85 (51.2)	229 (81.8)	<0.01	N/A	N/A	
Bone fracture/osteoporosis	20 (12.0)	31 (11.1)		N/A	N/A	
Nephrolithiasis	61 (36.7)	20 (7.1)		N/A	N/A	
Surgical procedure, n (%)						
Unilateral neck exploration	26 (15.7)	271 (96.8)	<0.01	7 (21.2)	6 (10.5)	0.02
FPTx	0 (0.0)	248 (88.6)		0 (0.0)	3* (5.3)	
Resection of two parathyroid glands	26 (15.7)	23 (8.2)		7 (21.2)	3 (5.3)	
Bilateral neck exploration	140 (84.3)	9 (3.2)		26 (78.8)	51 (89.5)	
Resection of one parathyroid gland	124 (74.7)	0 (0.0)		3* (9.1)	0 (0.0)	
Resection of three parathyroid glands	8 (4.8)	2 (0.7)		6 (18.2)	4 (7.0)	
TPTx with autotransplantation	8 (4.8)	7 (2.5)		17 (51.5)	47 (82.5)	
Histopathological diagnosis, n (%)						
Adenoma	151 (91.0)	270 (96.4)	<0.01	7 (21.2)	2 (3.5)	<0.01
Hyperplasia	15 (9.0)	9 (3.2)		24 (72.7)	55 (96.5)	
Carcinoma	0 (0.0)	1 (0.4)		2 (6.1)	0 (0.0)	
Recurrence	0 (0.0)	0 (0.0)		4 (12.1)	7 (12.3)	0.98
Permanent hypoparathyroidism, n (%)	2 (1.2)	4 (1.4)		7 (21.2)	31 (54.4)	0.35

*, diagnosed as sporadic PHPT at the time of initial surgery. PHPT, primary hyperparathyroidism; FPTx, focused parathyroidectomy; TPTx, total parathyroidectomy.

this period because the enlargement of multiple parathyroid glands was detected intraoperatively, and the possibility of hereditary PHPT could not be excluded. Although recurrence was not observed in the sporadic PHPT cases when bilateral exploration was performed, recurrence did not increase after bilateral exploration was discontinued.

The mean age tended to be younger in the last decade than that in the previous years for hereditary PHPT, although the difference was not significant (P=0.15). Furthermore, no significant difference was observed in the sex distribution (P=0.62) between the two groups. Concerning the histopathological diagnosis of enlarged parathyroid glands, a significant increase in adenomas in sporadic PHPT and hyperplasia in hereditary PHPT was observed after 2001 (P<0.01).

Analysis of recurrent cases of hyperparathyroidism

Overall, 11 out of 536 (2.1%) patients who had their first operation for PHPT at our hospital from 1986 to 2020 developed recurrent hyperparathyroidism. Among them, six were female and five were male, with ages ranging from 33–63 years (*Table 3*). The mean serum calcium and i-PTH levels in the recurrent cases were 11.1±0.5 mg/dL (range, 10.1–11.6 mg/dL) and 154.4±52.1 pg/mL (range, 85.1–238.6 pg/mL), respectively. Ten patients had a family

Table 3 Recurrent cases of PHPT after the operation

Patient No.	Age (years), sex	Initial diagnosis	Initial surgery	Total number of resected parathyroid	Time to recurrence (year)	Image examination	Site of recurrence	Preoperative calcium levels (mg/dL)	Preoperative intact PTH (pg/mL)	Recurrent diagnosis	Results of gene test
1	48, F	MEN1	FPTx	5	19.7	US, MRI	R/L, L/L	10.1	97.0	Adenoma	MEN1 (+)
2	52, F	MEN1	TPTx + AT	6	27.6	US, CT, MIBI	R/U, intrathyroid	11.4	183.4	Hyperplasia	MEN1 (+)
3	55, M	FIHP	Resection of two glands	5	12.6	CT, MIBI	Mediastinum	13.8	Not available	Carcinoma	Not tested
4	48, F	Adenoma	FPTx	4	20.8	US, CT, MIBI	R/U, L/U, intrathyroid	11.1	119.5	Hyperplasia	MEN1 (–), CDC73 (–)
5	61, M	MEN1	TPTx + AT	5	18.9	US, CT, MIBI, MRI	R/U	11.5	238.6	Hyperplasia	MEN1 (+)
6	63, F	MEN1	TPTx + AT	5	16.6	US, CT, MIBI	R/L†	11.0	85.1	Hyperplasia	MEN1 (+)
7	39, F	FIHP	Resection of three glands	4	12.5	US, CT, MIBI, MRI	L/L†	10.1	105.0	Carcinoma	MEN1 (–)
8	33, M	Adenoma	FPTx	3	2.5	US, CT, MIBI, MRI	R/U, R/L	10.8	190.5	Adenoma	CDC73 (+)
9	58, F	MEN1	Resection of two glands	5	2.9	US, CT, MIBI	R/U, L/U, L/L	11.2	380.0	Hyperplasia	MEN1 (+)
10	40, M	MEN1	TPTx + AT	5	2.4	CT, MIBI, MRI	Mediastinum	11.2	181.9	Hyperplasia	MEN1 (+)
11	49, M	MEN1	TPTx + AT	5	1.5	US, CT, MIBI, MRI	L/L†	11.6	130.9	Hyperplasia	MEN1 (+)

†, in the superior pole of the thymus. PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; MEN, multiple endocrine neoplasia; FIHP, familial isolated hyperparathyroidism; FPTx, focused parathyroidectomy; TPTx, total parathyroidectomy; AT, autotransplantation; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; MIBI, ^{99m}Tc-sestamibi scintigraphy; R/L, right lower; R/U, right upper; L/L, left lower; L/U, left upper.

history of PHPT or genetic abnormalities: seven were MEN1, two were FIHP, and one was HPT-JT. In the remaining case (case 4), post-recurrence examinations showed no findings suggestive of hereditary disease and no comorbidities that would cause parathyroid gland enlargement. A responsible parathyroid gland was identified in 10 of 11 cases through ^{99m}Tc-sestamibi scintigraphy. Nine patients had a recurrence in the neck, which was detected by CT or MRI and subsequently by the US. Enlarged parathyroid glands were found in the parathyroid area in six cases, in the intrathyroid gland in two cases, in the superior pole of the thymus in three cases, and in the mediastinum in two cases. Among the three cases with recurrence in the superior pole of the thymus, two were MEN1, and one was FIHP. In one patient with MEN1 and one with FIHP, ^{99m}Tc-sestamibi scintigraphy showed an accumulation in the anterior mediastinum, which was confirmed by CT or MRI.

The initial surgery was TPTx with autotransplantation of the parathyroid gland in five cases, FPTx in three, and resection of two glands in two, and resection of three in one. After recurrence, resection of the enlarged parathyroid glands was performed in all cases, and one patient with a recurrent parathyroid tumor in the mediastinum underwent video-assisted thoracic surgery. In seven patients, supernumerary (i.e., five or more) parathyroid glands were identified and removed ultimately, of which six patients had MEN1. The histopathological diagnoses of the parathyroid glands removed by reoperation were hyperplasia in seven patients, adenoma in two, and cancer in two. In one patient, the histopathological diagnosis of the parathyroid gland removed at the initial surgery was adenoma; however, the recurrent gland was diagnosed as hyperplasia. One patient with FIHP (case 3) and parathyroid cancer had four operations, including resection of lung metastases. Another patient with FIHP (case 7), who was the patient's daughter in case 3, required a third surgery. Although the causative gene mutation for the parent and child's PHPT was not identified, the daughter was diagnosed with FIHP from the absence of the MEN1 gene mutation and her clinical symptoms (15,16). Recurrence has not been

observed in the other cases thus far. On the other hand, the incidence of postoperative permanent hypoparathyroidism in patients with hereditary PHPT was 21.2% until the year 2000 and 54.5% after 2000, with no significant difference but a tendency to be more frequent in the latter period.

Discussion

The clinical presentation of PHPT in the United States and Europe has changed from symptomatic to asymptomatic over the past several decades following the prevalence of screening tests for serum calcium levels (17). However, most PHPT cases are still diagnosed based on the clinical symptoms in other parts of the world (5,18,19). To the best of our knowledge, there have been no English-language reports on the evolution of the clinical picture of PHPT in Japan. This study demonstrated an increase in asymptomatic PHPT at our institute, which is similar to that in the United States and Europe. Since our institution is located in a city in Japan with few other specialized hospitals and has been continuously treating patients with PHPT in the same area for the past 35 years, we believe that our analysis may represent the average evolution of the clinical picture of PHPT in Japan. Furthermore, we speculate that the increase in asymptomatic PHPT observed in our institute may reflect the prevalence of serum calcium level screening in health examinations at workplaces and voluntary health examinations in Japan (20,21).

For sporadic PHPT, bilateral cervical exploration to confirm that there was no other enlarged gland as determined by preoperative evaluation has long been performed in Japan. Subsequently, several studies have reported that removing the enlarged parathyroid gland alone results in a favorable clinical course with fewer recurrences (22), and FPTx has become the mainstay of treatment for sporadic PHPT (23). In addition, rapid measurement of serum i-PTH levels was available in the early 2010s, which has made the intraoperative evaluation of serum i-PTH levels possible (24,25). This test has enabled an objective determination of whether the parathyroid glands responsible for PHPT have been successfully removed, making FPTx more reliable in treating sporadic PHPT.

In addition, it is crucial to exclude the possibility of hereditary PHPT and identify the localization of the responsible parathyroid gland through diagnostic imaging before surgery to reduce recurrence after focused surgery. Although it is not difficult to suspect the presence of a hereditary disease, such as MEN, in patients with PHPT with a family history of urinary lithiasis or other symptoms, it is often difficult to differentiate whether their PHPT is sporadic or hereditary, particularly in young patients with PHPT with no family history. In our cohort, six patients were initially diagnosed with sporadic PHPT and underwent resection of one enlarged parathyroid gland alone; however, they were eventually diagnosed with hereditary PHPT due to the emergence of other symptoms and recurrent hypercalcemia. Hence, two patients subsequently underwent re-operation. Therefore, genetic testing should be considered more aggressively when the possibility of hereditary PHPT cannot be excluded.

As for the preoperative localization of the hyperfunctioning parathyroid glands, the detection rate of preoperative localization has improved with recent advances in diagnostic imaging, such as US, CT, MRI, and ^{99m}Tc-sestamibi scintigraphy (7-9). FPTx is considered for sporadic PHPT when the localization of the enlarged parathyroid is consistent with more than two imaging modalities performed preoperatively (10). Notably, the detection rate of hyperfunctioning parathyroid glands was approximately 100% when ^{99m}Tc-sestamibi scintigraphy was combined with CT or MRI (11). In the cohort analyzed in this study, the postoperative recurrence rate with sporadic PHPT was low. We have performed either CT and/or MRI together with US preoperatively in all PHPT cases. In addition, ^{99m}Tc-sestamibi scintigraphy has been used since 1995. Intraoperative rapid pathological diagnosis has already been used to confirm the parathyroid gland. In addition, intraoperative i-PTH measurements were also used since 2014. We believe that accurate preoperative localization through imaging diagnoses with multiple modalities and intraoperative pathological and biochemical diagnoses may have contributed to our institution's low postoperative recurrence rate (26,27). Recently, Di Marco *et al.* (28) reported that the recurrence rate of FPTx based on preoperative imaging diagnosis did not differ from that of bilateral neck exploration, even without concomitant intraoperative i-PTH measurement. Moreover, complications were significantly less with FPTx, which may reflect the advances in diagnostic imaging with the improved spatial resolution of CT, MRI, and US, enabling a more accurate localization of the hyperfunctioning parathyroid gland.

In our cohort, 12.2% of patients with hereditary PHPT had a recurrence. Parathyroid glands, usually four in number, are mostly found around the thyroid

gland. However, the frequency of excessive and ectopic parathyroid glands is 20–30% and 10%, respectively (13). Superior parathyroid glands originate from the fourth pharyngeal sac. Meanwhile, the inferior parathyroid gland originates from the third pharyngeal sac, which is the same as the thymus (14). The localization of the inferior parathyroid glands is widespread—24%, 2.2%, and 0.8% in the thymic tongue, anterior mediastinum, and thyroid gland, respectively, compared with 73.8% in the normal location—because they descend together with the thymic primordium (29,30). Therefore, we resected the thymic tongues on both sides when four parathyroid glands could not be identified by carefully exploring the perithyroid area. However, identifying non-enlarged parathyroid glands outside the perithyroid region was difficult in the primary operation, and hyperfunctioning parathyroid could sometimes be found in unexpected regions in recurrent cases. In the cohort analyzed in this study, we could identify recurrent hyperfunctioning parathyroid glands by ^{99m}Tc-sestamibi scintigraphy in 10 of the 11 recurrent cases, including in the mediastinum in two of them. Thus, since the parathyroid glands may be located in a wide area from the neck to the mediastinum, ^{99m}Tc-sestamibi scintigraphy is useful in identifying the parathyroid glands, particularly in recurrent PHPT cases.

Because of the increased risk of recurrent laryngeal nerve palsy by reoperation for the peri-thyroid region, recurrent surgery for PHPT should be avoided as much as possible. However, our analysis demonstrates that FPTx is an appropriate procedure for sporadic PHPT with a low recurrence rate when preoperative diagnostic evaluations and intraoperative are examined appropriately.

On the other hand, we cannot ignore permanent hypoparathyroidism as a postoperative complication of PHPT. Permanent hypoparathyroidism has developed in more than half of the hereditary PHPT cases since 2001. This increased incidence of permanent hypoparathyroidism might be partly because more patients underwent TPTx. Furthermore, this might be due to changes in the volume of autologous parathyroid glands since the surgeons at our institution have been replaced during the 35-year time period. Therefore, the results of this study suggest that we should reevaluate the volume of parathyroid glands to be autologously transplanted to reduce the incidence of permanent hypoparathyroidism.

A limitation of this study is that we cannot exclude the possibility that the accuracy of diagnosis in older cases might differ from that of recent cases as the methods and accuracy of endocrinological and genetic testing have changed over the past 35 years, and several pathologists have performed the histological diagnosis regardless of a single-center analysis. Therefore, in the future, it will be necessary to conduct genetic testing for sporadic PHPT cases as much as possible to accurately diagnose the disease type and decide on a treatment strategy.

Conclusions

Our study demonstrated that FPTx is considered an appropriate procedure for sporadic PHPT that has been carefully examined preoperatively. In the future, it will be necessary to conduct genetic testing for sporadic PHPT cases as much as possible to accurately diagnose the disease type and decide on a treatment strategy to prevent a postoperative recurrence of PHPT.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the clinical investigation ethics committee of Shinshu University (No. 4501). The requirement for informed consent was waived since this was a retrospective study of anonymized data. This study complied with the provisions of the Declaration of Helsinki (as revised in 2013).

References

1. Fraser WD. Hyperparathyroidism. Lancet 2009;374:145-58.
2. Wilhelm SM, Wang TS, Ruan DT, et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. JAMA Surg 2016;151:959-68.
3. Walker MD, Silverberg SJ. Primary hyperparathyroidism. Nat Rev Endocrinol 2018;14:115-25.
4. Marcocci C, Cetani F. Update on the use of cinacalcet in the management of primary hyperparathyroidism. J Endocrinol Invest 2012;35:90-5.
5. Bilezikian JP, Silverberg SJ. Clinical practice. Asymptomatic primary hyperparathyroidism. N Engl J Med 2004;350:1746-51.
6. Bilezikian JP, Bandeira L, Khan A, et al. Hyperparathyroidism. Lancet 2018;391:168-78.
7. Parikh AM, Grogan RH, Morón FE. Localization of Parathyroid Disease in Reoperative Patients with Primary Hyperparathyroidism. Int J Endocrinol 2020;2020:9649564.
8. Tay D, Das JP, Yeh R. Preoperative Localization for Primary Hyperparathyroidism: A Clinical Review. Biomedicines 2021.
9. Hoang JK, Sung WK, Bahl M, et al. How to perform parathyroid 4D CT: tips and traps for technique and interpretation. Radiology 2014;270:15-24.
10. Ramirez AG, Shada AL, Martin AN, et al. Clinical efficacy of 2-phase versus 4-phase computed tomography for localization in primary hyperparathyroidism. Surgery 2016;160:731-7.
11. Lorberboym M, Minski I, Macadziob S, et al. Incremental diagnostic value of preoperative 99mTc-MIBI SPECT in patients with a parathyroid adenoma. J Nucl Med 2003;44:904-8.
12. Wimmer G, Profanter C, Kovacs P, et al. CT-MIBI-SPECT image fusion predicts multiglandular disease in hyperparathyroidism. Langenbecks Arch Surg 2010;395:73-80.
13. Liechty RD, Weil R 3rd. Parathyroid anatomy in hyperplasia. Arch Surg 1992;127:813-5; discussion 815-6.
14. Akerström G, Malmaeus J, Bergström R. Surgical anatomy of human parathyroid glands. Surgery 1984;95:14-21.
15. Guan B, Welch JM, Sapp JC, et al. GCM2-Activating Mutations in Familial Isolated Hyperparathyroidism. Am J Hum Genet 2016;99:1034-44.
16. Marx SJ. New Concepts About Familial Isolated Hyperparathyroidism. J Clin Endocrinol Metab 2019. [Epub ahead of print]. doi: 10.1210/jc.2018-02789.
17. Pallan S, Rahman MO, Khan AA. Diagnosis and management of primary hyperparathyroidism. BMJ 2012;344:e1013.
18. Muthukrishnan J, Hari Kumar KV, Jha R, et al. Distal renal tubular acidosis due to primary hyperparathyroidism. Endocr Pract 2008;14:1133-6.
19. Yadav SK, Mishra SK, Mishra A, et al. Changing Profile of Primary Hyperparathyroidism Over Two and Half Decades: A Study in Tertiary Referral Center of North India. World J Surg 2018;42:2732-7.
20. Overview of the 2010 National Survey of Living Conditions: Ministry of Health, Labor, and Welfare in Japan. Available online: https://www.mhlw.go.jp/toukei/saikin/hw/k-tyosa/k-tyosa10/3-5.html
21. Overview of the 2019 National Survey of Living Conditions: Ministry of Health, Labor, and Welfare in Japan. Available online: https://www.mhlw.go.jp/toukei/saikin/hw/k-tyosa/k-tyosa19/dl/14.pdf
22. Carling T, Udelsman R. Focused approach to parathyroidectomy. World J Surg 2008;32:1512-7.
23. Jinih M, O'Connell E, O'Leary DP, et al. Focused Versus Bilateral Parathyroid Exploration for Primary Hyperparathyroidism: A Systematic Review and Meta-analysis. Ann Surg Oncol 2017;24:1924-34.
24. Irvin GL 3rd, Dembrow VD, Prudhomme DL. Clinical usefulness of an intraoperative "quick parathyroid hormone" assay. Surgery 1993;114:1019-22; discussion 1022-3.
25. Barczynski M, Konturek A, Hubalewska-Dydejczyk A, et al. Evaluation of Halle, Miami, Rome, and Vienna intraoperative iPTH assay criteria in guiding minimally invasive parathyroidectomy. Langenbecks Arch Surg 2009;394:843-9.
26. Rohaizak M, Munchar MJ, Meah FA, et al. Prospective study comparing scrape cytology with frozen section in the intraoperative identification of parathyroid tissue. Asian J Surg 2005;28:82-5.

27. Dewan AK, Kapadia SB, Hollenbeak CS, et al. Is routine frozen section necessary for parathyroid surgery? Otolaryngol Head Neck Surg 2005;133:857-62.
28. Di Marco A, Mechera R, Glover A, et al. Focused parathyroidectomy without intraoperative parathyroid hormone measurement in primary hyperparathyroidism: Still a valid approach? Surgery 2021;170:1383-8.
29. Edis AJ, Purnell DC, van Heerden JA. The undescended "parathymus". An occasional cause of failed neck exploration for hyperparathyroidism. Ann Surg 1979;190:64-8.
30. Billingsley KG, Fraker DL, Doppman JL, et al. Localization and operative management of undescended parathyroid adenomas in patients with persistent primary hyperparathyroidism. Surgery 1994;116:982-9; discussion 989-90.

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