Original Article

Clinical characteristics of primary parathyroid adenoma and its relationship with coexisting papillary thyroid carcinoma: a clinical retrospective study

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Background: Parathyroid adenoma (PA) is a common but relatively poorly understood endocrine tumor. A significant number of PA patients also have papillary thyroid carcinoma (PTC). The clinicopathological characteristics of PA and its relationship with PTC need further study.

Methods: The clinical data of 99 PA patients were reviewed and the clinicopathologic features of PA were analyzed. PTC occurred in 22 PA patients. The clinicopathologic features of 22 patients with PA + PTC and 77 patients with PA alone were compared. According to age, gender and thyroid surgery methods, 22 PA + PTC patients were matched with 1,123 patients with PTC alone during the same period. The pathological characteristics of the two groups of patients were compared. All data analysis was performed using SPSS23.0, variables were compared by *t*-test, chi square test or Mann Whitney U-test as appropriate.

Results: Ninety-nine PA patients (21 males, 78 females) with a median age of 51 [10–80] years were included. The preoperative parathyroid hormone (PTH) (P=0.007) and preoperative blood calcium (P=0.036) of male patients were higher than those of female patients, and the proportion of asymptomatic patients (P=0.008) and postoperative PTH level (P=0.013) were lower. The preoperative PTH level (P=0.002), preoperative blood calcium level (P=0.004), preoperative alkaline phosphatase (ALP) level (P=0.018) and postoperative PTH levels (P=0.023) in PA + PTC group were lower than those in PA group. The asymptomatic rate was higher in PTC + PA group than that in PA group (P<0.001). There was no statistical difference between PA + PTC group and PTC group in multifocal tumor, capsule invasion, lymph node metastasis (P>0.05). The lymph node metastasis rate in PA + PTC group (9/215) was significantly lower than that in PTC group (37/337) (P=0.005).

Conclusions: PA exhibited the following characteristics: occurred in all age groups; more common in women but more severe in men; more located in the lower pole. The coexistence of PTC and PA did not promote the progression of PA, nor did it increase the aggressiveness of PTC. Conversely, their co-existence may lead to early diagnosis of the disease. PA patients (22.2%) also have PTC, so surgeons should pay attention to thyroid disease to prevent the need for reoperation.

Keywords: Papillary thyroid carcinoma (PTC); parathyroid adenoma (PA); parathyroid hormone; primary hyperparathyroidism (PHPT)

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Introduction

Primary hyperparathyroidism (PHPT) is the third largest endocrine disease after diabetes and thyroid disease. It is a systemic disease characterized by calcium and phosphorus metabolism disorder caused by excessive secretion of parathyroid hormone (PTH) due to parathyroid gland disease (1). PHPT has various clinical manifestations, mainly involving the kidney and skeletal system, including kidney stones, bone pain, limb deformities, pathological fractures. Other symptoms include nausea and vomiting, chronic pancreatitis, limb weakness and mental abnormalities (2). With the popularity of blood electrolytes and PTH laboratory tests, the number of patients with hyperparathyroidism has been increasing in the past decade, especially asymptomatic patients. The incidence of PHPT is higher in women than in men, and gender differences in incidence become apparent with age (3). But there is a lack of epidemiological statistics on PHPT in China.

The common etiology of PHPT includes parathyroid adenoma (PA), parathyroid hyperplasia and parathyroid carcinoma (PC), with solitary PA accounting for the highest proportion, about 80% (4). There is no single pharmacological treatment that can address the skeletal and renal consequences of hypercalcemia and PHPT. Surgery is the only effective treatment to cure PA, which is recommended for patients with symptomatic or subclinical end-organ involvement (such as bone and kidney) (5). Here, the perioperative data and follow-up data of patients with PA treated by our center were statistically analyzed, the surgical effects and postoperative complications of patients were analyzed, and the clinical characteristics of PA were summarized.

According to previous literature reports, the proportion of PHPT patients with accompanying thyroid diseases is relatively high, which can reach more than 50% (6). The study of Çetin *et al.* indicated that the presence of PHPT may increase the aggressiveness of papillary thyroid carcinoma (PTC) (7,8). In this study, 22 (22.2%) PA patients had PTC at the same time. Considering the anatomical adjacency of thyroid and parathyroid glands, the coexistence of both may affect the treatment decision. Therefore, the relationship between PA and PTC was analyzed and discussed. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-635/rc).

Highlight box

Key findings

- Primary adenoma (PA) occurs in all age groups; more common in women but more severe in men; more located in the lower pole. The coexistence of papillary thyroid carcinoma (PTC) and PA did not promote the progression of PA, nor did it increase the aggressiveness of PTC.

What is known and what is new?

- The incidence of primary hyperparathyroidism (PHPT) is higher in women. Patients with PHPT often have coexisting thyroid disease.
- Male patients with PA have higher levels of serum calcium and PTH, and more severe clinical symptoms. PA are more common in the lower pole. The coexistence of PA and PTC will not lead to the progress of the two diseases

What is the implication, and what should change now?

- Since a considerable number of PA patients coexist with PTC, surgeons should pay attention to screening disease before surgery to avoid the need for secondary surgery.

Methods

Patient enrollment

Ninety-nine patients who underwent initial surgical treatment and were confirmed as PA by postoperative pathology from January 1, 2016 to December 31, 2021 in Wuhan Union Hospital were included. Exclusion criteria: multiple endocrine adenomatosis (MEN); secondary hyperparathyroidism (due to renal insufficiency, intestinal calcium malabsorption) or tertiary hyperparathyroidism (due to hyperphosphatemia, renal transplantation); pregnant women; major organ failure; combined with other malignant tumors except PTC; important information missing. Twenty-two patients with PA also had PTC. The biochemical levels and clinical manifestations of patients with PA and PTC were compared with those of patients with PA alone to study the effect of PTC on PA. Case-control matching in SPSS23.0 software (match tolerances 0 for all) were used to match 22 PA + PTC patients from 1,123 patients with PTC (pathological diagnosis confirmed and excluding other malignancies and severe organ dysfunction) who were operated on during the same period. We obtained 22 pairs of eligible subjects and compared their pathological differences to study the effect of PA on PTC.

Data collection

Information collected included: age, gender, height, weight, urinary ultrasound, bone mineral density, thyroid and

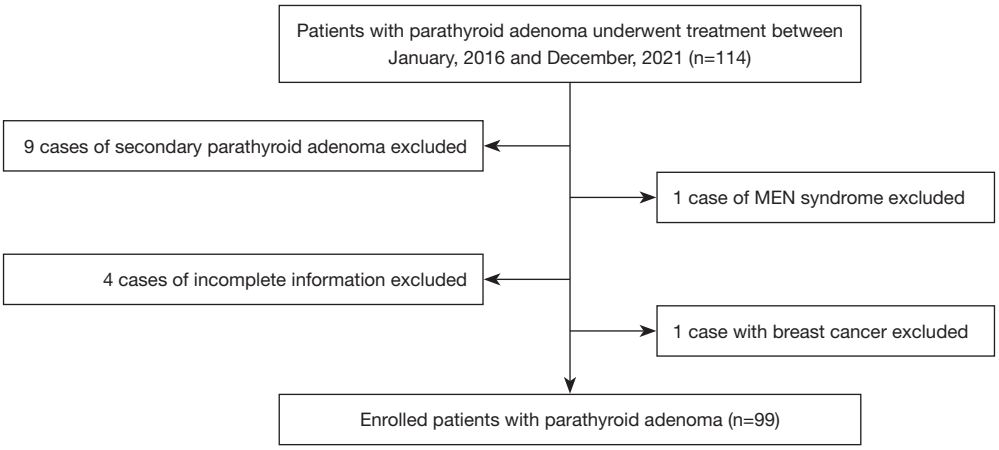

Figure 1 The flow diagram for enrolling of patients with parathyroid adenoma. MEN, multiple endocrine neoplasia.

parathyroid ultrasound, blood PTH, blood electrolyte, and blood alkaline phosphatase (ALP). All the blood samples were fasting blood samples, and the postoperative blood samples were taken in the morning of the first day after the operation.

Surgical indications and methods

Surgical indications included: symptomatic patients, asymptomatic patients with bone and kidney damage, patients with indications for thyroid surgery and suspected PA, no contraindication of operation, obtaining informed consent. All PA patients underwent complete tumor resection through neck incision. All patients with PTC underwent hemithyroidectomy or total thyroidectomy and central lymph node dissection. The thyroid surgery methods of PTC patients mainly include the following three types: lobectomy and isthmectomy + unilateral central lymph node dissection, lobectomy and isthmectomy + bilateral central lymph node dissection, total thyroidectomy + bilateral central lymph node dissection. Patients were given prophylactically intravenous 1,000 mg calcium gluconate supplementation after operation. Patients take calcium orally (calcium 1,500 mg+ vitamin D3 15 μg) when they can eat, and adjust the dose according to the patient's condition.

Definition

Asymptomatic hyperparathyroidism is defined as those patients who lack the bone and kidney manifestations described in the classic PHPT (9). The persistence of PHPT is defined as hypercalcemia within 6 months after parathyroidectomy, and the recurrence of PHPT is defined as hypercalcemia after normal blood calcium interval more than 6 months after parathyroidectomy (10).

Statistical analysis

All statistical analyses were conducted using SPSS version 23.0 (SPSS, Inc., Chicago, IL, USA). The measurement data were expressed as mean (± standard deviation) for continuous variables or median (min–max) for non-normally distributed variables; The counting data was expressed in the number of cases (percentage). The normality of data distribution was assessed by the Kolmogorov-Smirnov test. Variables were compared by *t*-test, chi square test or Mann Whitney U-test as appropriate. Two-tailed $P<0.05$ was considered statistically significant.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was exempt from the approval processes of the Institutional Review Boards because no personal information about patients were sought, and their identity would not be revealed in any publication. Individual consent for this retrospective analysis was waived.

Results

Of the 114 patients whose medical records were reviewed, 99 patients were included (*Figure 1*). There were 21 males

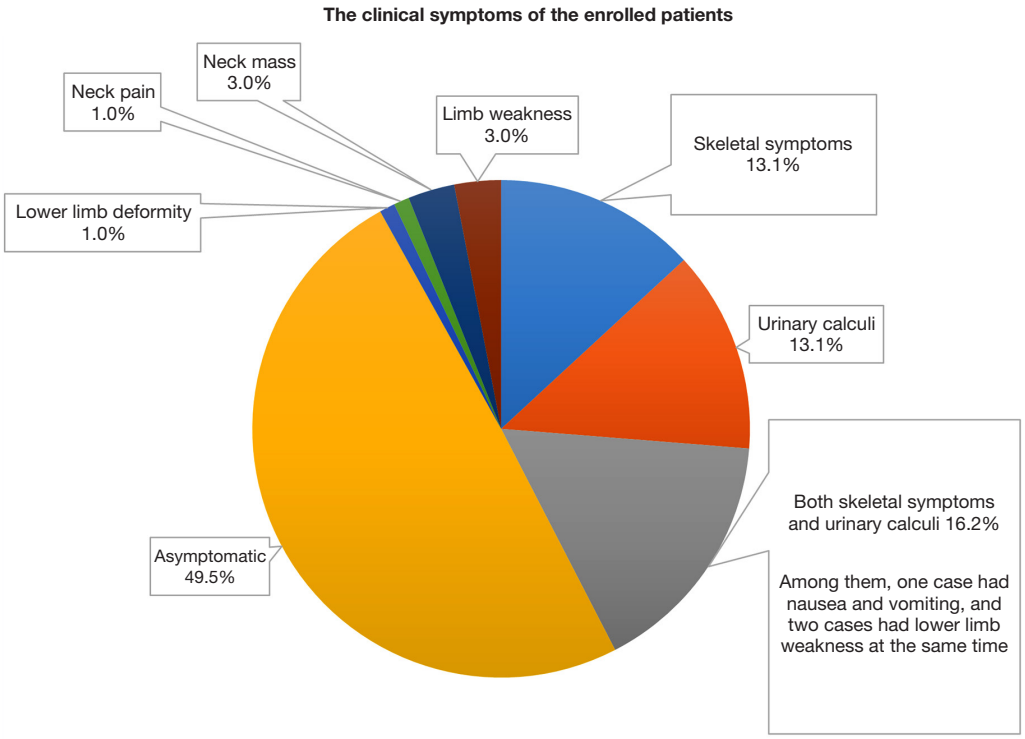

Figure 2 The clinical symptoms of the enrolled patients.

and 78 females, with the ratio of 1:3.7, the median age was 51 [10–80] years old.

Patients had different clinical manifestations: 13 (13.1%) cases had bone pain or bone destruction; 13 cases (13.1%) had urinary calculi; 16 (16.2%) patients presented with bone and urinary system symptoms at the same time, of which 3 (3.0%) patients presented limb weakness and 1 (1.0%) patient presented nausea and vomiting; in addition, 3 (3.0%) patients had simple limb weakness, 3 (3.0%) patients found neck mass, 1 (1.0%) patient suffered from neck pain, and a 10-year-old boy had lower limb deformity; 49 (49.5%) patients were asymptomatic, 26 asymptomatic cases found PA due to thyroid disease, 23 cases found hyperparathyroidism or mass in parathyroid region during physical examination (*Figure 2*).

There were 98 cases of single parathyroid tumor and 1 case of multiple parathyroid tumors (*Table 1*). The median size of a parathyroid tumor was 16 mm (range, 5–70 mm), the largest PA was 70 mm in diameter which located in the thyroid gland. Total resection of PA through a curved incision in the neck was performed in all cases, of which 44 cases were combined with thyroidectomy, including 22 cases of hemithyroidectomy and 22 cases of total thyroidectomy. PTC was present in 22 patients (22.2%).

There was no difference in age and body mass index (BMI) between the male and female groups (*Table 2*). The proportion of asymptomatic patients in male patients (23.8%) was lower than that in female patients (56.4%) (P=0.008). Preoperative PTH level was significantly higher in the male group [559.90 (99.90–3,000.00) pg/mL] than in the female group [233.15 (63.90–3,000.00) pg/mL] (P=0.007). At the same time, preoperative blood calcium level of male patients [2.88 (2.12–3.99) mmol/L] was also higher than that of female patients [2.62 (2.18–5.80) mmol/L] (P=0.036). The postoperative PTH level of male group [16.40 (1.60–58.10) pg/mL] was lower than that in female group [32.62 (1.00–207.5) pg/mL] (P=0.013).

There was no significant difference in age and sex between PA + PTC group and PA group (*Table 3*). The preoperative PTH level [PA + PTC *vs.* PA, 183.60 (63.90–528.86) *vs.* 322.60 (72.10–3,000.00) pg/mL, P=0.002], preoperative blood calcium level [PA + PTC *vs.* PA, 2.54 (2.18–2.97) *vs.* 2.69 (2.12–5.80) mmol/L, P=0.004], preoperative ALP level [PA + PTC *vs.* PA, 94.00 (28.00–191.00) *vs.* 116.00 (48.00–3,354.00) U/L, P=0.018] and postoperative PTH levels [PA + PTC *vs.* PA, 21.40

Table 1 Clinicopathological characteristics of PA patients

Variable	Overall (n=99)	%
Sex		
Male	21	21.2
Female	78	78.8
Age[a] (years)	51 [10–80]	
<30	8	8.1
30–39	13	13.1
40–49	20	20.2
50–59	41	41.4
≥60	17	17.2
BMI[b] (kg/m^2)	22.10 (±3.43)	
Clinical manifestations		
Symptomatic	50	50.5
Asymptomatic	49	49.5
Detection means		
99mTc-MIBI[c]	71/73	97.3
Ultrasound[c]	64/99	64.6
Surgery[c]	17/–	
Tumor location		
Left upper pole	16	16.2
Left lower pole	35	35.4
Right upper pole	19	19.2
Right lower pole	28	28.3
Within thyroid gland	1	1
Tumor size[a] (mm)	16 [5–70]	
Thyroid surgery	44	44.4
Hemi-thyroidectomy	22	22.2
Total thyroidectomy	22	22.2
Concomitant thyroid cancer		
Yes	22	22.2
No	77	77.8

[a], median (min–max); [b], mean (± standard deviation); [c], positive/cases of examined (percentage). PA, primary adenoma; BMI, body mass index.

(1.00–89.20) *vs.* 30.40 (2.80–207.50) pg/mL, P=0.023] in PA + PTC group were lower than those in PA group. The asymptomatic rate was higher in PTC + PA group than that in PA group (P<0.001).

In order to compare the relationship between PA and PTC, we included 22 PTC patients during the same period matched by gender, age and thyroid surgical method in this study.

There was no statistical difference in multifocal tumor, capsule invasion, lymph node metastasis (P>0.05). However, the lymph node metastasis rate in PA + PTC group (9/215) was significantly higher than that in PTC group (37/337) (P=0.005) (*Table 4*).

Follow-up

Ninety-five of the 99 patients were followed up for 41 [9–80] months. The follow-up contents included measurement of PTH and blood electrolyte, ultrasound and 99mTc-MIBI performed when necessary. No patient had disease recurrence or died.

Discussion

In this retrospective study, we observed the age, sex, clinical symptoms, blood biochemical level and other basic information of 99 PA patients, compared the clinicopathological characteristics of patients of different genders, and analyzed the interaction between PA and PTC, which may provide reference for the diagnosis and treatment of PA in the future.

Similar to thyroid disease, the incidence rate of PA in women is higher than that in men. However, male PA patients have higher preoperative PTH and preoperative blood calcium levels, which may be the reasons for male to shows more severe symptoms. Male PA patients shows a higher proportion with symptoms, which also confirms this opinion (*Table 2*). Excessive PTH secretion by PA may cause the secretion function of other normal parathyroid to be inhibited (11). After tumor surgery, the normal parathyroid gland needs a certain time to recover its secretory function. Male PA patients secrete more PTH before surgery and shows stronger inhibitory function, which may be the reason for the lower PTH in male patients after surgery.

In all patients, the lowest preoperative blood calcium was 63.90 pg/mL, which was within the normal reference range. The patient's blood calcium was 2.29 mmol/L, which was also a normal value. He was hospitalized in our hospital because of thyroid nodules. However, preoperative thyroid ultrasound found a nodule with a diameter of about 12 mm on the dorsal side of the left lobe of the thyroid

Table 2 Clinicopathological differences between male and female PA patients

Variable	Male (n=21)	Female (n=78)	P
Age[a] (years)	50 [10–79]	51 [21–80]	0.196
BMI[b] (kg/m^2)	22.54 (±3.89)	21.98 (±3.31)	0.509
Symptomatic/asymptomatic	16/5	34/44	0.008*
Preoperative PTH[a] (pg/mL)	559.90 (99.90–3,000.00)	233.15 (63.90–3,000.00)	0.007*
Preoperative calcium[a] (mmol/L)	2.88 (2.12–3.99)	2.62 (2.18–5.80)	0.036*
Preoperative phosphorus[a] (mmol/L)	0.69 (0.38–0.87)	0.73 (0.40–1.90)	0.058
Preoperative ALP[a] (U/L)	125.00 (58.00–3,354.00)	105.50 (28.00–1,662.00)	0.163
Postoperative PTH[a] (pg/mL)	16.40 (1.60–58.10)	32.62 (1.00–207.50)	0.013*
Postoperative blood calcium[a] (mmol/L)	2.15 (1.80–2.84)	2.13 (1.73–2.99)	0.366
Postoperative blood phosphorus[a] (mmol/L)	0.74 (0.49–1.26)	0.88 (0.44–1.77)	0.015*

[a], median (min–max); [b], mean (± standard deviation). *, P<0.05. Normal range: PTH, 15–65 pg/mL; blood calcium, 2.08–2.60 mmol/L; blood phosphate, 0.80–1.60 mmol/L; ALP, 15–112 U/L. PA, primary adenoma; BMI, body mass index; PTH, parathyroid hormone; ALP, alkaline phosphatase.

Table 3 Comparison of the clinical and biochemical features of PA concomitant PTC and classic PA groups

Variable	PA + PTC (n=22)	PA (n=77)	P
Age[a] (years)	50.5 [36–65]	51 [10–80]	0.990
Male/female	2/20	19/58	0.200
BMI[a] (kg/m^2)	23.86 (16.77–36.87)	21.45 (14.02–28.39)	<0.001*
Symptomatic/asymptomatic	4/18	46/31	<0.001*
Preoperative PTH[a] (pg/mL)	183.60 (63.90–528.86)	322.60 (72.10–3,000.00)	0.002*
Preoperative blood calcium[a] (mmol/L)	2.54 (2.18–2.97)	2.69 (2.12–5.80)	0.004*
Preoperative blood phosphorus[a] (mmol/L)	0.85 (0.58–1.15)	0.72 (0.38–1.90)	0.018*
Preoperative ALP[a] (U/L)	94.00 (28.00–191.00)	116.00 (48.00–3,354.00)	0.018*
Postoperative PTH[a] (pg/mL)	21.40 (1.00–89.20)	30.40 (2.80–207.50)	0.023*
Postoperative blood calcium[a] (mmol/L)	2.10 (1.73–2.49)	2.14 (1.78–2.99)	0.232
Postoperative blood phosphorus[a] (mmol/L)	0.90 (0.63–1.65)	0.82 (0.44–1.77)	0.071

[a], median (min–max). *, P<0.05. Normal range: PTH, 15–65 pg/mL; calcium, 2.08–2.60 mmol/L; phosphate, 0.80–1.60 mmol/L; ALP, 15–112 U/L. PA, parathyroid adenoma; PTC, papillary thyroid carcinoma; BMI, body mass index; PTH, parathyroid hormone; ALP, alkaline phosphatase.

gland, which was suspected to be an enlarged parathyroid gland. Due to the abnormal imaging findings before the operation, we explored the parathyroid gland during thyroidectomy and found an enlarged parathyroid gland in the lower left pole. We partially removed the mass and sent it to rapid pathology. The pathology suggested PA, so we performed complete mass resection. Although the patient's preoperative PTH and electrolyte levels were normal, he would eventually present PHPT because the pathological change of his parathyroid gland (12). The evaluation of the possibility of hyperparathyroidism should not rely solely on PTH level, but should be combined with blood calcium, blood phosphorus level and even parathyroid imaging findings.

Surgical removal of tumor is the final treatment for PA patients at present. Symptomatic patients should be treated

Table 4 Difference in pathological characteristics between PA concomitant PTC and classical PTC

Pathological features	PA concomitant PTC (n=22)	PTC (n=22)	P
Tumor size[a] (mm)	5 [0.5–13]	5 [2–35]	0.795
Multifocal[b] (+/%)	5/22.7%	10/45.5%	0.112
Capsule invasion[b] (+/%)	10/45.5%	11/50%	0.763
LN metastasis[b] (+/%)	3/13.6%	7/31.8%	0.150
LN metastasis rate[c]	9/215	37/337	0.005*

[a], median (min–max); [b], number of positive patients/percentage; [c], number of lymph nodes with cancer metastasis/number of the patients' lymph nodes dissected. *, P<0.05. PA, parathyroid adenoma; PTC, papillary thyroid carcinoma; LN, lymph nodes.

surgically, which can reduce the risk of urinary tract stones and fractures, reduce the risk of cardiovascular disease and death, and significantly improve the quality of life of patients (13,14). However, it is still controversial whether asymptomatic patients should receive surgery. As PA is a benign tumor with a risk of continuous development, some asymptomatic patients may eventually develop clinical symptoms in the natural history of the disease, which will greatly affect the quality of life. Zanocco *et al.* found that PA resection resulted in cost savings and improved quality of life in patients with mild or asymptomatic PHPT compared to observation (15). Therefore, patients with PHPT suspected of PA should also be more active in the consideration of undergoing surgery. According to the previous guidelines and article summary (10,16), the following patients with PHPT are recommended to undergo surgery: symptomatic patients; asymptomatic patients with target organ damage (such as severe osteoporosis, renal function damage, etc.); patients younger than 50 years old. If any of the following occurs in asymptomatic PHPT patients who needs thyroid surgery, it is recommended to actively explore bilateral parathyroid glands during the surgery: preoperative hypercalcemia, high PTH, Preoperative imaging revealed enlarged parathyroid glands or dorsal thyroid nodules.

Patients with PA (whether or not surgery is performed) should have regular biochemical tests every 3–6 months, including PTH, blood calcium, blood phosphorus, kidney function, kidney stone risk, and bone mineral density. More than 1/3 of the postoperative recurrence cases of PA occurred more than 10 years after the operation, so long-term postoperative follow-up should also be conducted (17).

The conventional surgical method is PA resection through neck arc incision. It is worth mentioning that because it is difficult to distinguish parathyroid gland from adipose tissue, we tend to completely remove PA and some adipose tissue around it to ensure the integrity of the envelope and prevent tumor residue. In patients with a single parathyroid tumor, the incidence of lower pole parathyroid tumor (63.6%) is higher than that of upper pole parathyroid tumor (35.4%) (*Table 1*). The lower pole parathyroid gland can move down with the thymus during development, and its position changes greatly, which makes it more difficult for surgeons to find the parathyroid gland surgically (18). According to Lu *et al.*, the most common site of ectopic PA is in the superior mediastinum (52.1%), and most of this type can be treated by surgery in the thyroid region alone (19). However, nearly half of PAs located elsewhere require combined thoracic or abdominal surgery. Therefore, preoperative imaging examination is very important for tumor localization. Common imaging examination includes 99mTc-MIBI and ultrasound examination. In our center, the positive rate of ultrasound for parathyroid tumor was 64.6%, and the positive rate of 99mTc-MIBI imaging for parathyroid tumor was 97.3%. 99mTc-MIBI has higher diagnostic significance for parathyroid tumors. When there is interference of thyroid diseases or changes, it is difficult to observe parathyroid gland by ultrasound (20). Therefore, 99mTc-MIBI should be actively performed in patients with hyperparathyroidism suspected PA.

There were 22 (22.2%) cases of PA patients accompanied by PTC. In PA + PTC group, the preoperative PTH levels, preoperative blood calcium levels, preoperative ALP levels and postoperative PTH levels were lower than those in classic PA group. The proportion of asymptomatic patients in PA + PTC group was higher (*Table 3*). These two points jointly suggest that the coexistence of PA and PTC will not lead to the aggravation of PA symptoms. On the contrary, the presence of PTC may lead to the early diagnosis of PA.

Hu *et al.* found that PTC showed more malignant pathological features and early recurrence in patients with changes in internal environment (such as solid organ

transplantation) (21,22). Beebeejaun *et al.* speculated the interaction mechanism of PA and PTC in his article, high PTH level, Hypercalcemia and low 1,25 Dihydroxyvitamin D may lead to the growth and aggressivity of PTC (23). According to the data of our center, there was no statistical difference between PA + PTC group and PTC group in multifocal tumor, capsule invasion, lymph node metastasis (P>0.05) (*Table 4*). Concomitant PA did not make PTC more aggressive, which is contrary to the opinions of Jeong and Çetin (7,8). Meanwhile, the lymph node metastasis rate of PA + PTC group was lower than that of PTC group, which confirmed our previous view that the coexistence of PA and PTC may lead to the early detection of disease. Since a considerable number of PA patients also suffer from PTC, preoperative screening for thyroid disease should be paid attention to in PHPT patients to avoid the need of reoperation.

There are several limitations that should be acknowledged. Firstly, the sample size of the study is relatively small, which may weaken the results. Secondly, since it is a retrospective study, there are inherent selection biases and uncontrollable confounding factors. Meanwhile, due to the long-time span and incomplete examination, vitamin D content, urinary calcium and other data are missing, making it difficult to conduct further analysis.

Conclusions

PA is more common in women, but more symptomatic in male patients. The tumor is more common in the lower pole. The existence of PA and PTC The co-presence of PA and PTC does not lead to the progression of PTC or PA, but may lead to early detection of the disease. Because of the high incidence rate of PTC in PA, surgeons should pay attention to thyroid diseases when performing PA surgery in order to avoid the need of reoperation.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-635/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-22-635/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-635/coif). The authors have no conflicts of interest to declare.

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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was exempt from the approval processes of the Institutional Review Boards because no personal information about patients were sought, and their identity would not be revealed in any publication. Individual consent for this retrospective analysis was waived.

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