

## Case Report

# Surgical diagnosis and treatment of primary hyperparathyroidism: analysis of 19 cases

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**Abstract:** This study was to discuss the surgical diagnosis and treatment experience of primary hyperparathyroidism. Clinical data of 19 primary hyperparathyroidism patients who were treated surgically in our department from Jan. 2005 to Jul. 2014 were retrospectively analyzed. Besides, general data, clinical manifestations, laboratory and imaging test results, surgical procedures and postoperative follow-up information were comprehensively analyzed. 15 of 19 patients had adenoma, among whom 1 case was complicated with goiter, 3 cases with parathyroid hyperplasia, and 1 case with parathyroid carcinoma. One case of bilateral parathyroid adenoma was explored bilaterally, and the bilateral parathyroid adenoma was excised. 14 cases of unilateral parathyroid adenoma were explored unilaterally and the unilateral parathyroid adenoma was excised. 3 cases of parathyroid hyperplasia were explored bilaterally, and parathyroid glands were removed subtotally, and only half gland was reserved. 1 case of parathyroid carcinoma experienced excision of thyroid gland and parathyroid at the affected side and isthmus excision, subtotal excision of thyroid gland at the healthy side and functional cervical lymphonode dissection at the affected side. All the 19 cases recovered well after operation, and symptoms of hyperparathyroidism were controlled. No relapse was found after follow-up of 3 months to 5 years. In conclusion, local parathyroid excision with small wounds after pre-operative locative image test and qualitative laboratory test is effective. Timely surgical treatment could reduce joint and urinary damage. Post-operative follow-up should be emphasized for early detection of the patients with hypoparathyroidism and recurrence.

**Keywords:** Hyperparathyroidism, diagnosis, therapeutics

## Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disease, mainly characterized by calcium-phosphate metabolism disorder, bone and (or) urinary system disorder. The symptoms are caused by elevated auto-secretion of parathyroid hormone (PTH) due to parathyroid adenoma, hyperplasia or carcinoma. This disease is often misdiagnosed or mistreated as many organ systems are involved, such as cardiovascular, bone, urinary, and neural system, etc [1, 2]. Early diagnosis and appropriate surgical treatment are very important for treating this disease. The clinical research of PHPT has progressed a lot since Mandle performed the first parathyroid excision in 1925. Especially in the recent 10 years, the clinical diagnosis and treatment level of this disease has a great improvement with the progression of parathy-

roid anatomy, embryology, and pathophysiology. However, the clinical misdiagnosis and mistreatment of this disease still occur. This article retrospectively analyzed the clinical data of 19 PHPT patients treated by our department from Jan. 2005 to Jul. 2014, and the details were summarized as follows.

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A total 19 patients were enrolled in our group (3 males, 16 females), with an average age of 46 years (27-75 years). The duration of disease ranged from 23 days to 11 years. 15 cases in our group had adenoma, among whom, 1 case was combined with goiter, 3 cases with parathyroid hyperplasia, and 1 case with parathyroid carcinoma. Among 15 adenoma patients, 14 cases had unilateral lesion with only one ectopic lesion, and the remained one case was

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**Table 1.** The percentage of general data and clinical manifestations of patients

Classification of general data and clinical manifestations		Cases (n, %)	
Gender	Male	3 (15.8)	
	Female	16 (8.4)	
Pathological type	Adenoma	14 (73.7)	
	Adenoma combined with goiter	1 (5.3)	
	Parathyroid hyperplasia	3 (15.8)	
	Parathyroid carcinoma	1 (5.3)	
Pathogenic sites	Right	5 (26.3)	
	Left	9 (47.4)	
	Bilateral	1 (5.3)	
	Ectopic	1 (5.3)	
	Multifocal	3 (15.8)	
Clinical manifestations	Asymptomatic	1 (5.3)	
	Urinary system symptom	Urolithiasis	9 (47.4)
		Ureteral calculus on the left side combined with hydronephrosis	1 (5.3)
		Urinary irritation	2 (10.5)
		Hematuria	1 (5.3)
	Bone and Joint disorder	Joint pain	7 (36.8)
		Pathologic fracture of lumbar spine	1 (5.3)
		Systemic osteoporosis	1 (5.3)
	Joint pain combined with renal calculus	2 (10.5)	
	Headache, Dizziness, Nausea, Vomiting	1 (5.3)	

**Table 2.** Results of image test of hyperparathyroidism

Test method	Positive	Negative	Relevance Ratio (%)	Diseased location	
				Normal site	Abnormal site
B Ultrasound (n=19)	15	4	78.9	15	0
CT (n=13)	11	2	84.6	10	1
SPECT (n=7)	6	1	85.7	5	1

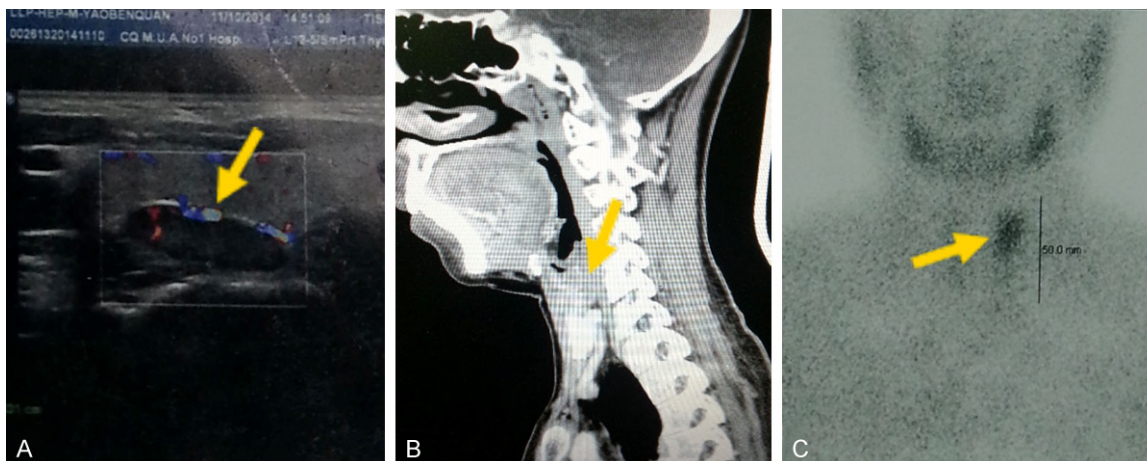
found to have bilateral lesion. The parathyroid hyperplasia was multifocal. 5 cases exhibited right-sided adenomas, and 8 cases showed left-sided adenomas while 1 case suffered from bilateral adenomas. The ectopic one was at the middle of lower pole of the right thyroid gland.

Only 1 adenoma patient in our group had no symptom. 9 cases were found to be accompanied by urinary calculus, among whom 1 adenoma case was combined with left ureteral calculus and hydronephrosis, 2 cases with urinary irritation, 1 case with hematuria. 7 patients were found to have joint pain, including 1 case with lumbar spinal pathological fracture, 1 case with systemic osteoporosis, 2 cases with joint pain and renal calculus. Furthermore, 1 para-

thyroid carcinoma patient reported symptoms as headache, dizziness, nausea and vomiting when getting up in the morning. See **Table 1.**

Serum calcium test was performed in 19 patients. According to the results, serum calcium level obviously increased in 18 cases, with an average of 3.25 mmol/L (2.68-4.61 mmol/L). One case had a serum calcium level of 2.21 mmol/L, which was a little lower than the normal value. Urinary calcium was elevated in 15 patients, with an average value of 8.13 mmol/L and the highest value of 16.92 mmol/L. Serum phosphate decreased in 18 patients, with the lowest value of 0.45 mmol/L and an average of 0.67 mmol/L, most below 0.6 mmol/L. Only one case had normal serum phosphate. In 11 patients among the 19 ones, serum alkaline phosphatase (ALP) obviously increased, with the highest value of 5 times the upper limit of normal value.

Elevated parathyroid hormone (PTH) occurred in 19 patients, ranged from 500-2100 pg/ml (normal range: 20-50 pg/ml). And their thyroid



**Figure 1.** Findings of B-ultrasonic testing, CT and SPECT scan of parathyroid. A: Longitudinal B-ultrasonic image of parathyroid adenoma at upper left. Arrow showed oval hypoecho mass posterior to the left lobe of thyroid gland with a size of 2.1 × 1.2 cm, homogeneous cytoplasm, well-defined boundary and visible capsule. B: Sagittal CT image of parathyroid adenoma at upper right. The arrow showed isopycnic mass posterosuperior to the right lobe of thyroid gland, with a size of 0.9 × 0.6 cm and well-defined boundary. The adenoma showed enhancement after contrast agent injection, but the enrichment degree was lower than that of normal thyroid gland. C: Delay-phase SPECT image of parathyroid adenoma at upper left. The arrow showed that the nodule superior to the thyroid gland was continuous, while the development the lower left lobe and the whole right lobe was reduced.

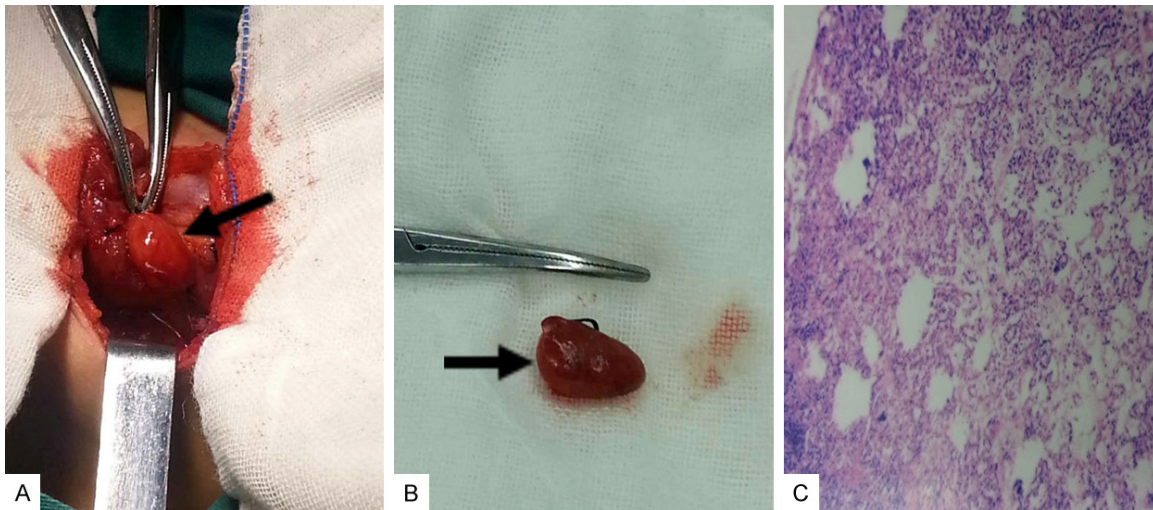
functions were all normal. Ultrasonic examination was conducted in 19 patients, including enhanced CT scan in 13 cases and parathyroid SPECT image test in 7 cases. See **Table 2** and **Figure 1**.

All patients were treated surgically. Parathyroid adenomas in 15 patients were resected, including the right parathyroid adenoma in 8 cases, the left parathyroid adenoma in 5 cases, bilateral parathyroid adenoma in 1 case, and ectopic parathyroid adenoma in 1 case. Three patients received hyperplastic parathyroidectomy. 1 case of parathyroid carcinoma received excision of thyroid and parathyroid at the affected side and isthmus excision, subtotal excision of thyroid at the healthy side and functional cervical lymphonode dissection at the affected side.

14 out of 15 cases had unilateral adenoma, and the remaining one suffered from bilateral adenoma. The distribution of unilateral adenoma was as follows: 3 at upper right pole, 2 at lower right pole, 4 at upper left pole, 4 at lower left pole, and the ectopic one at the middle of the lower right lobe (about 0.8 cm). The largest adenoma was 5.0 cm × 5.8 cm, while the smallest was 0.9 cm × 1.2 cm. The bilateral adenoma patient received bilateral adenoma excision, but the remaining received unilateral exploration and adenoma excision. Among 3

patients with parathyroid hyperplasia, one who was diagnosed with adenoma had received parathyroid gland excision in our hospital in 2001, but didn't improve after operation. The serum calcium and PTH of this patient elevated continuously in the recent 2 years. During this examination, through careful exploration of the reverse side of bilateral thyroid glands, 2 hyperplastic parathyroid glands were found. Finally, 1.5 glands were excised, and only 0.5 glands were reserved. In the other two patients having an intraoperative frozen section pathological report of parathyroid hyperplasia, 0.5 right glands were reserved, and the remaining were excised. The situation of the two patients improved after the operation. One patient was found to have parathyroid carcinoma at the lower pole of left lobe, and excision of left thyroid and parathyroid and isthmus excision, subtotal excision of right thyroid and left functional cervical lymphonode dissection was done. 15 patients were diagnosed by the intraoperative frozen section pathology, among whom, 3 patients were confirmed to have parathyroid hyperplasia, and one patient was diagnosed with parathyroid carcinoma. The intraoperative situation and postoperative pathology were presented in **Figure 2**.

None of the 19 cases exhibited the surgery-related complications such as hoarseness or bucking. 10 cases suffered from numbness of



**Figure 2.** Intraoperative situation and postoperative pathology. A: Arrow showed the parathyroid adenoma posterior to left lobe of thyroid gland, which was yellowish-brown, with well-defined boundary. B: Arrow showed the complete parathyroid adenoma excised in panel D, with size of 2 × 1 cm, well-defined boundary and complete capsule. C. Showed the microscopic findings of paraffin section of parathyroid adenoma: the adenoma cells were sheet in arrangement, mainly including enlarged chief cells with large and hyperchromatic nuclei; sporadic eosinophil cells and acinar or pseudoglandular pattern could be seen.

face and extremities within 3 days after the surgery. In 2 cases experiencing transient tetany, the previous symptoms remitted after daily intravenous injection of calcium gluconate 10-30 ml, oral administration of 1-2 calcium carbonate D3 tablets twice to four times a day, and calcitriol 0.25ug once or twice a day to maintain the serum calcium level above 1.90 mmol/L. All of 19 patients received 3-month to 5-year follow-up after the surgery. As a result, they all exhibited normal range of serum calcium, relieved clinical manifestations at different degrees, improved osteoporosis and healing fracture. Besides, it was also found that bone pain disappeared in six cases and relieved in one case, and none showed the sign of recurrence. One patient with parathyroid carcinoma did not experienced recurrence or metastasis during 5-years follow-up.

## Discussion

### *Screening high-risk population of PHPT*

The high-risk population of PHPT includes patients with recurrent urinary calculus, osteoporosis, unexplained skeletal deformity, spontaneous fracture, unexplained lumbocrucral pain and ulcers who are unresponsive to routine therapy, especially the young people. Because the early symptoms of PHPT are not

typical, misdiagnosis and mistreatment is easily led to. What is more, the urinary and skeletal damage of PHPT patients couldn't be recovered completely even if the primary lesion is excised. Therefore, the early diagnosis was very important [3]. The critical questions in improving the diagnosis and treatment level of PHPT lie in screening of high-risk patients, enhancing of cognitive level about PHPT and improving of early diagnosis rate. The longest duration from onset to diagnosis was 5 years in these 19 patients. Among them, 9 cases were misdiagnosed with urinary calculus, urinary infection, RA, osteoporosis, fracture, bone tumor, etc., respectively. Correspondingly, 3 cases of them received nephrolithotomy, and the others all suffered from improper therapies. Therefore, the possibility of PHPT should be considered once the patients exhibited the symptoms or signs of systemic joints pain, osteoporosis, pathological fracture and multiple urinary calculi. In order to improve the early diagnosis rate of PHPT, we proposed the suggestions below: 1) The following patients should be recognized as the high-risk population of PHPT in outpatient department: those with unexplained chronic lumbocrucral pain, recurrent and multiple urinary calculus, ulcers and acute pancreatitis who were unresponsive to routine therapy. 2) The serum calcium test should be conducted routinely. 3) The serum calcium,

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serum phosphate, serum choline, alkaline phosphatase of subjects to be screened should be detected. Because of the intermittent elevation of patients' serum calcium, serum calcium must be detected repeatedly. Serum PTH or  $Cl/P^{3-}$  ratio should be tested to identify PHPT or hypercalcemia caused by other origins.

### *Qualitative and localization diagnosis of PHPT*

*Qualitative diagnosis:* laboratory test is the major defining characteristic of qualitative diagnosis. The clinical diagnosis is mainly based on hypercalcemia, hypophosphatemia, elevated urinary calcium (24 h-Ca > 200 mg), and elevated PTH [4]. But under some special circumstances, the serum calcium is not elevated. Some late PHPT patients may exhibit normal serum calcium, therefore, serum free calcium and PTH could be detected to certify the diagnosis of PHPT [5]. Meanwhile, other causes of increased serum calcium should be excluded. 18 out of 19 cases in our group were characterized as evaluated serum calcium, among whom 1 case was found serum calcium increased when receiving routine test, and 12 cases were diagnosed with PHPT through further detection of elevated PTH. If the qualitative diagnosis is not certified pre-operatively, the pathological examination with fine needle aspiration under ultrasonic guidance might be helpful.

*Localization diagnosis:* the common methods of localization diagnosis include B ultrasound, CT and SPECT scan. B ultrasound could be the first choice for its convenience, and the experienced tester and high frequency probe could provide a more accurate pre-operative localization diagnosis. Enhanced CT scan is suitable for ectopic localization and specific for parathyroid adenoma especially; but it may show negative results for the smaller lesions. SPECT scan is effective in ectopic parathyroid adenoma positioning, but very expensive. In the present study, we compared the value of B ultrasound, CT and SPECT scan applied in pre-operative localization diagnosis, and the results showed that the positive rates of the three techniques in localization were 78.95%, 84.62%, and 85.71%, respectively. This means that at least 3/4 of the parathyroid adenoma could be found by these routine tests, and the positive rate can be up to more than 90% if the three methods are combined. We think that B ultrasound could be used as the first choice for localization

of PHPT patients, and B ultrasound combined with CT and SPECT could make the localization more accurate and may determine a relationship between lesions and thyroid gland with peripheral tissues. Other traumatic localization methods, such as angiography, DSA, segmental selective venous blood sampling, are not recommended as routine test ways.

All the 19 patients were misdiagnosed or mistreated before they were diagnosed definitely by our hospital, with the longest duration of misdiagnosis of up to 5 years. Among the 19 cases, 9 cases were misdiagnosed with urinary calculus, urinary infection, RA, osteoporosis, fracture, and bone tumor. Correspondingly, 3 cases received nephrolithotomy, the others experienced the improper treatments. All the patients were confirmed with PHPT based on medical history, laboratory test (serum calcium and elevated blood PTH) and image test before operation.

### *Surgery indications*

Surgery is the only effective way treating hyperparathyroidism. The absolute surgery indications are symptomatic PHPT and suspected parathyroid carcinoma. For the asymptomatic patients, the surgery is necessary if any one of the following indications is met: (1) Serum calcium was 1.0 mg/dL higher than the normal upper limit. (2) CCr was over 30% lower than the normal lower limit. (3) 24 hour-urinary calcium > 400 mg. (4) T-score of bone mineral content (lumbar spine, bone joints, forearm) showed more than -2.5SD decrease. (5) Aged > 50 years old. (6) Patients who were hard or unwilling to receive routine follow-up [6]. In clinical work, the accuracy of pre-operative localization and qualitative diagnosis, operative procedure selection and the experience of the operator should be considered.

### *Operative procedure selection*

It remains controversial whether the patient should receive unilateral or bilateral cervical exploration. The presence of multiple adenomas supports the bilateral exploration. But 80%~85% of the primary PHPT are caused by adenoma, while most of parathyroidoma are single (80%). Of the remaining patients, 10% are caused by glands hyperplasia, and only 2%~4% are caused by multiple adenoma, even

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of which 40% are homolateral. If adenoma is confirmed by the pre-operative localization diagnosis of single tumor or the enhanced parathyroid pathological frozen section, unilateral exploration could be feasible on the basis of excluding the familial or multiple MEN I [7]. The indications of bilateral exploration are as follows: multiple enlarged glands found in pre-operative image test, hyperplasia by intraoperative pathological frozen section, MEN-1, indistinguishable gland during operation, atypical locations of glands, difficult definition of the upper or lower gland found during operation. In the present study, 15 of 19 patients with adenoma were single, and only one had bilateral adenomas. Moreover, the operation was performed smoothly and very effective. Therefore, it is feasible to explore unilaterally in most of patients. To prevent that the actually existed multiple parathyroid adenomas are not explored by image tests, many researchers suggested intraoperative isotope detection and intraoperative rapid detection of PTH [8, 9]. It would indicate a complete excision of lesion if PTH decreases by more than 50% at 10 minutes after the lesion excision compared with the pre-operative value. If the intraoperative frozen section shows parathyroid hyperplasia, the bilateral 4 glands must be explored and excised. According to our experience, at least 3.5 glands must be excised, or 4 glands could be excised; then 0.5~1 gland is taken for autotransplantation. 1 case in our group received 3.5 glands excision and the 0.5 excised gland was autotransplanted in the muscle of the forearm to prevent the hypocalcemia. If there was still hypercalcemia, the gland in the forearm could be removed. It is very convenient and reliable to control the number of glands excised. The operation procedure of papillary thyroid carcinoma can be referred to for the treatment of parathyroid carcinoma

### *Treatment of ectopic parathyroid lesion*

The occurrence rate of ectopic parathyroid gland was 14% to 26%, mainly including adenoma or hyperplasia. If pre-operative localization cannot be done and the intraoperative bilateral exploration showed negative result, ectopic parathyroid lesion should be considered. Ectopic parathyroid lesion usually occurs at the supraclavicular fossa, next to carotid artery, at the substernal area and in the mediastinum. If the lesion couldn't be found in the intraopera-

tive exploration, radionuclide method was an alternation [10]. The lesion in one case of ectopic parathyroid adenoma located in the middle of right lower lobe of the thyroid gland (about 0.8 cm) was noted through this method, and was excised smoothly. If the parathyroid glands couldn't be found in the normal sites, the usual ectopic sites must be considered. The ectopic upper parathyroid glands usually locate in the parenchyma of thyroid glands, pharyngeal and retroesophageal region. While the ectopic lower parathyroid glands usually occurs at the middle and anterior mediastinum of thymus in the lower neck.

### *Treatment of parathyroid crisis*

The parathyroid crisis is very rarely seen. There was a report that only 1-2% PHPT patients had parathyroid crisis during treatment [11]. As for our group, only one case had parathyroid crisis. The diagnosis of parathyroid crisis is based on three essential conditions: confirmation of PHPT, serum calcium > 3.75 mmol/L and occurrence of crisis symptoms in clinic, such as the symptoms in gastrointestinal tract, cardiovascular system, nerve and muscle. The death rate from parathyroid crisis without immediate treatment could be as high as 60% [12]. Gasparri et al. [13] analyzed retrospectively the clinical data of 36 patients with parathyroid crisis, and believed it necessary to perform early operation before severe cardiovascular, urinary and neuromuscular failure occurred. Without primary lesion resection, it was very hard to alleviate the disease only through conservative medical treatment. We believe that the immediate operation after proper preparation is safe and effective. One parathyroid crisis patient in our group received short-term hemodialysis treatment, and then underwent emergent surgery of adenoma after the serum calcium < 3.5 mmol/L; at last, this patient recovered well. If the patient is intolerable for surgery, internal treatment must be taken to control the condition, and the surgery could be performed after the condition is stable. However, the preparation time shouldn't be too long, the surgery must be done decisively if the condition is not improved.

Local parathyroid excision with small wounds after pre-operative locative image test and qualitative laboratory test is effective. Timely surgical treatment could reduce joint and uri-

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nary damage. Post-operative follow-up should be emphasized on early detection of the patients with hypoparathyroidism and recurrence.

### Disclosure of conflict of interest

None.

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