

# Surgical treatment of primary hyperparathyroidism due to parathyroid tumor: A 15-year experience

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**Abstract.** The aim of this study was to highlight our experience over a 15-year period in dealing with primary hyperparathyroidism (PHPT) due to a parathyroid tumor. Parathyroidectomy is the standard therapy for patients with PHPT. Our study included all patients with PHPT treated by parathyroidectomy at the Affiliated Cancer Hospital of Zhengzhou University, China. Between 1998 and 2013, a total of 107 patients were recruited. Their clinical data, presentation, laboratory examinations, imageological diagnoses and surgical approaches were analyzed retrospectively. Eighty-four cases (78.5%) were followed up. During a median follow-up period of 5.7 years, a total of 80 patients were without recurrence and metastasis. The main symptoms of PHPT patients were palpable neck mass, joint pains and pathological fracture. The high levels of preoperative parathyroid hormone (PTH) and serum calcium in PHPT patients decreased to below the normal upper limit within 3 days of surgery. The sensitivity of neck ultrasonography, sestamibi scanning, CT, MRI and the combination of three or four types of test were 86.0%, 90.4%, 80.8%, 79.6% and 96.1%, respectively. A 50% or greater drop in PTH levels within 20 min compared with the highest PTH levels before surgery occurred in 95/107 cases (88.8%). Transient hypocalcemia was the most common surgical complication. The ultrasonography and sestamibi scan is the most effective examination for parathyroid tumor. The 20 min PTH measurement appears to be extremely useful, and avoids unnecessary bilateral exploration.

## Introduction

Primary hyperparathyroidism (PHPT) is characterized by hypercalcemia resulting from the overproduction of parathyroid hormone (PTH) by one or multiple hyperfunctioning parathyroid glands. It is the third most common endocrine disorder with a reported incidence of ~0.25% in the general population (1). The incidence of PHPT increases with age, and it occurs more frequently in females than in males (2). Research has confirmed that the majority of patients with PHPT require surgery due to the risk of renal stones, osteoporosis, cardiovascular disease, and in certain cases silent complications of renal impairment (3). The majority of PHPT cases are caused by a single parathyroid adenoma (75-85% of cases) (4). In 1928, Dr. Isaac Olch (5) performed the first successful parathyroidectomy at Barnes Hospital in St. Louis, MO, USA, and currently this operation remains one of the most effective treatments, providing great potential for cure in patients with PHPT. As the clinical features of PHPT are variable and lack specificity, there is no clear consensus with regard to the most effective treatment of patients with the condition. Therapeutic strategies generally arise through clinical experiences. In this study, we report our experience of dealing with 107 cases of PHPT due to parathyroid tumor over the past 15 years, as well as our experience in treatment of the condition with parathyroidectomy.

## Materials and methods

**Patient data.** In this retrospective study, we recruited 107 patients who were operated on for PHPT in our surgical department between January 1998 and December 2013. Of the 107 patients, there were 80 females and 27 males, with a median age of 57 years (range, 28-79 years). The disease duration ranged from 6 months to 15 years (median, 25 months). Clinical information was derived from a thorough review of the medical records and the institutional patient database. Follow-up data were obtained through correspondence and outpatient department visits, with the average follow-up period being 5.7 years (range, 1-15 years).

**Presentation and diagnosis.** Forty-three patients exhibited an asymptomatic neck mass. Metabolic bone disease was radiologically observed in 37 cases. Nineteen patients were

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**Abbreviations:** PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; CT, computed tomography; MRI, magnetic resonance imaging; IOPTH, intraoperative parathyroid hormone

**Key words:** primary hyperparathyroidism, parathyroidectomy, parathyroid, parathyroid hormone, intra-operative parathyroid hormone

Table I. Sensitivity and positive predictive values for various preoperative diagnostic modalities.

Index	Ultrasound (%)	Sestamibi (%)	CT (%)	MRI (%)	Association of ultrasound and sestamibi (%)
Sensitivity	86.0	90.4	80.8	79.6	94.7
Positive predictive value	95.3	94.1	83.6	85.0	100.0

CT, computed tomography; MRI, magnetic resonance imaging.

asymptomatic despite hypercalcemia. Eighteen were initially observed to have constitutional symptoms including palpitations, nausea, fatigue, weight loss and memory deficit. Twelve patients exhibited lithanguria but had normal renal function. Several patients suffered more than one symptom.

To localize hyperfunctioning parathyroid glands, a variety of imaging techniques were used, including neck ultrasonography, Tc-99 m sestamibi scanning, computed tomography (CT) and magnetic resonance imaging (MRI). All patients underwent neck ultrasonography. The Tc-99 m sestamibi scan was performed in 83 cases (77.6%). In addition, 47 patients accepted CT or MRI scanning.

**Treatment.** Under general anesthesia, all our cases underwent a focused parathyroidectomy associated with a rapid intraoperative PTH (IOPTH) assay monitoring. PTH levels were measured prior to parathyroid tumor excision, and subsequent post-excision measurements followed at 10 and 20 min, if a sufficient reduction in PTH value was not observed. A 50% or greater drop in PTH values from the pre-incision or pre-excision level was considered to indicate a surgical success.

**Ethics.** Ethical approval was granted from the Zhengzhou University Ethical Review Board.

## Results

**Pathological presentation.** A total of 104 patients (97.2%) had benign lesions, and 3 patients (2.8%) had parathyroid carcinoma. Of the 104 patients, there were 97 cases (90.7%) of single parathyroid adenoma, 4 cases (3.7%) of multiple parathyroid adenoma or combined parathyroid hyperplasia, and 3 cases (2.8%) of parathyroid hyperplasia. Eighty-four cases (78.5%) were followed up. During the follow-up period, 2 patients (2.4%) suffered parathyroid adenoma recurrence, 2 patients (2.4%) succumbed to parathyroid carcinoma, 1 case of carcinoma survived for 34 months before succumbing to postoperative lung and bone metastasis, and 1 succumbed to a cardiovascular accident 21 months after surgery. The remaining patients did not experience recurrence or metastasis.

**Sensitivity and positive predictive values.** Ultrasonographic examination of the neck revealed 92 cases of occupied lesions in the parathyroid gland and 10 cases in the thyroid gland (Fig. 1). The remaining 5 cases had normal neck ultrasonography results. The sensitivity and positive predictive values were 86.0% and 95.3%, respectively. Eighty-three patients underwent Tc-99 m sestamibi scanning. The accumulation

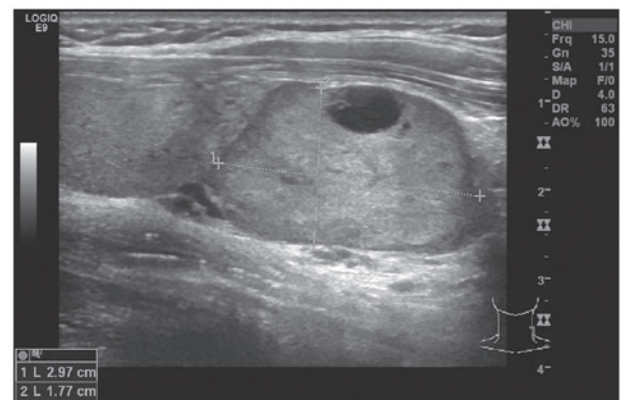


Figure 1. Ultrasound image of a parathyroid adenoma.

of radioactivity was observed in 75 of these patients (Fig. 2). The sensitivity and positive predictive values were 90.4% and 94.1%. The combination of an ultrasound and 99 m Tc-sestamibi scan localized hyperfunctioning parathyroid in 76/82 patients (92.7%). The sensitivity in identifying parathyroid tumors by CT and MRI was 80.8% and 79.6%, respectively (Table I).

**PTH levels.** Prior to surgery, elevated PTH levels were observed in all patients. The preoperative serum calcium was abnormally elevated in 86 patients (80.4%). The levels of serum calcium and PTH in patients with parathyroid hyperplasia and carcinoma were significantly higher than those in parathyroid adenoma patients (Table II).

A 50% or greater drop in PTH levels within 10 min compared with the highest PTH levels before surgery occurred in 86 patients (80.4%). In 9 cases the >50% drop in PTH levels was attained after 20 min (8.4%). A >50% drop in PTH levels within 20 min was achieved by 95/107 patients (88.8%; Table III).

**Complications.** Surgical complications were observed in nine patients: three had wound infections, two had hematoma necessitating re-operation and two had transient recurrent laryngeal nerve paresis. Transient hypocalcemia occurred in 19 cases (17.8%). Symptoms ranged from face, hand and foot numbness to limb twitching. All of these patients were treated with calcium and vitamin D per os and intravenously with resolution within 1 month. There were no cases of permanent hypocalcemia.

**Statistical analysis.** Results were recorded and are expressed as the means  $\pm$  standard deviation. Statistical significance

Table II. Comparison of observed indices among various pathological parathyroid lesions.

Index	Parathyroid adenoma (n=101)	Parathyroid hyperplasia (n=3)	Parathyroid carcinoma (n=3)
PTH before surgery (pmol/l, mean $\pm$ SD)	121.3 $\pm$ 29.0	143.0 $\pm$ 76.3 <sup>a</sup>	188.2 $\pm$ 56.5 <sup>b</sup>
Serum calcium before surgery (mmol/l, mean $\pm$ SD)	2.9 $\pm$ 0.4	3.3 $\pm$ 0.6 <sup>c</sup>	4.3 $\pm$ 1.9 <sup>d</sup>

<sup>a</sup>P=0.004; <sup>b</sup>P=0.001; <sup>c</sup>P=0.005; <sup>d</sup>P=0.000, compared with parathyroid adenoma. PTH, primary hyperparathyroidism; SD, standard deviation.

Table III. Decrease in PTH following surgery.

Decrease in PTH	>50% decrease in PTH within 10 min	>50% decrease in PTH after 20 min
Patients	86.0	9.0
%	80.4	8.4

PTH, primary hyperparathyroidism.

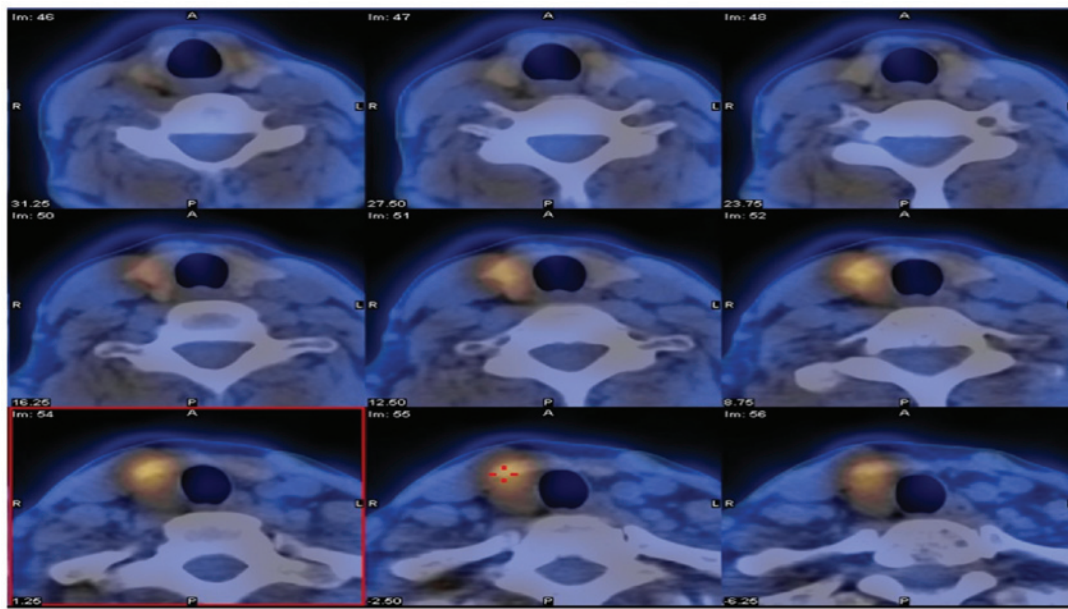


Figure 2. Strong accumulation of Tc-99 m in the right thyroidal lobe was observed.

was determined using the Chi-square test. All analyses were performed using the Statistical Package for Social Science (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA).  $P < 0.05$  was considered to indicate a statistically significant difference.

## Discussion

Ruda *et al* (6) reviewed of the diagnosis and treatment of PHPT from 1995 to 2003 and concluded that single parathyroid adenoma accounts for ~90% of benign tumors of the parathyroid. Our study revealed a similar result: 90.7% of our cases had single-gland disease.

The diagnosis of PHPT is generally made biochemically following the measurement of elevated serum calcium and

PTH levels (1,4). In this group, we did not observe any significant differences between the parathyroid hyperplasia and the parathyroid carcinoma groups with regard to the PTH and serum calcium values before surgery. However, the levels of serum calcium and PTH in patients with parathyroid hyperplasia and carcinoma were significantly higher than those of parathyroid adenoma patients. However, the small sample size of three cases means that the study should be replicated with a larger sample.

There is wide variation in the anatomic location of the parathyroid glands, and in certain patients hyperfunctioning glands are hard to locate during surgery. In these cases, reliable preoperative localization of abnormal parathyroid glands has become invaluable. The two most common imaging



modalities are sestamibi scanning and neck ultrasonography. High-resolution ultrasound is an effective examination to locate enlarged parathyroid glands in the neck. One of the advanced features of neck ultrasound is the ability to study the thyroid gland concurrently for any abnormalities. In addition, neck ultrasound is also beneficial as it is inexpensive, it does not use ionizing radiation, and it has high sensitivity (7). The sensitivity of ultrasonography for the localization of abnormal parathyroid glands generally varies in the literature from 61% to 85% (8-11). However, in the present study, we noted a higher sensitivity of 86.0%. The variation in these numbers could be due to the fact that ultrasonography is operator-dependent. At our institution, ultrasonography is performed by a professional neck ultrasound doctor, and these individuals are likely to have the best understanding of neck anatomy. Much like ultrasonography, sestamibi also has a high sensitivity for the detection of abnormal parathyroid glands, and is particularly useful in detecting small, posterior adenomas (12). According to our statistical results, when ultrasound and sestamibi scans are used together, the sensitivity of preoperative localization of parathyroid adenomas increases. These findings are consistent with the majority of studies. The reported sensitivity ranges between 94% and 99% (13). CT and MRI are less used but are useful in patients with failed parathyroidectomy or persistent PHPT to identify ectopic glands (8).

In their study on the reassessment of PTH monitoring, Gawande *et al* (14) noted that it is less necessary to monitor the value of IOPTH when there are concordant imaging studies. Conversely, other studies (15) advocate the use of IOPTH monitoring to guide parathyroid excision in all patients with PHPT.

Sokoll (16) argued that using IOPTH in conjunction with reliable preoperative localization facilitates the ability to perform minimally invasive surgery in an ambulatory surgery setting with improved success intraoperatively, increased patient satisfaction postoperatively, and decreased costs perioperatively. This argument has been a hot debate in the literature in recent years and is likely to continue to be a point of discussion in the foreseeable future. However, from our point of view, surgical treatment without IOPTH assay may be appropriate in certain institutions where financial or access constraints prevent the use of IOPTH assay, and at this point, how to correctly locate the abnormal parathyroid glands is particularly significant.

At our institution, IOPTH assay is still widely used. In particular, blood collection timing appears to be a critical step (17). The widely used Miami criterion (rapid IOPTH value drop >50% from the highest levels either pre-incision or at 10 min after gland excision) is reported to have a high overall accuracy. However, other authors have reported error rates as high as 16% due to false-negative and false-positive results (18). They suggested that 20 min of PTH monitoring should be performed (19). In this study, we performed IOPTH monitoring after 10 min if a >50% drop of PTH levels was not observed. In nine patients (6.4%), a >50% decrease of PTH was observed only after 20 min, and an unnecessary bilateral exploration was thus avoided.

Cure of PHPT may be defined as normocalcemia 6 months after surgery, irrespective of the level of PTH (20).

According to Hessman *et al*, the success rate of parathyroidectomy is greater than 95%, with low complication rates in cases performed by experienced surgeons (21). The results of the present study are similar to those of Hessman *et al* (21).

Parathyroid carcinoma is an extremely rare malignancy and is reported to occur in less than 0.1% to 5% of patients with PHPT (22-24). The same result was demonstrated in the current study. There were 3 cases of parathyroid carcinoma (2.8%) among the 107 cases of PHPT due to parathyroid tumor in our study. To date, the diagnostic criteria for parathyroid carcinoma has been inconsistent. Parathyroid carcinoma may therefore be under- or overdiagnosed. In our experience, the obscure boundary or/and invasion of adjacent tissues is the key indicator of parathyroid carcinoma. For parathyroid carcinoma, males and females are equally affected, usually in the fourth or fifth decade of life. Short of a major biological or molecular breakthrough, surgery remains the most effective therapeutic and palliative option (25).

Considering the small number of parathyroid carcinoma cases, our clinical diagnostic and treatment experience is limited. Further research is required on this topic to confirm our findings.

In conclusion, the symptoms of PHPT vary and lack specificity. Parathyroidectomy provides the most effective treatment for PHPT due to parathyroid tumor. The ultrasonography and sestamibi scan is the most effective examination for parathyroid tumor. The 20 min PTH measurement appears to be extremely useful, and avoids unnecessary bilateral exploration and the associated risk of complications with only a slight increase in the duration of surgery and the cost.

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