

# Coexistence of Papillary Thyroid Carcinoma in Secondary Hyperparathyroidism

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## Research article

**Keywords:** papillary thyroid carcinoma, secondary hyperparathyroidism, tumor characteristics, morbidity, occult papillary thyroid carcinoma, Retrospective Case-Control Study

**Posted Date:** January 15th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-145242/v1>

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# Abstract

**Background:** Coexistence of primary hyperparathyroidism and papillary thyroid carcinoma is common and may be associative with more aggressive papillary thyroid carcinoma for higher rates of extrathyroidal extension and multicentricity. However, it remains unclear whether secondary hyperparathyroidism accounts for more invasive papillary thyroid carcinoma in terms of morbidity, tumor pathological characteristics and prognosis. The aim of this study was to evaluate the rate and tumor characteristics of papillary thyroid carcinoma in patients of SHPT.

**Methods:** A total of 531 patients diagnosed of SHPT and underwent surgery were evaluated retrospectively from January 2013 to December 2018 in the first affiliated hospital of the Zhejiang University. Patients' demographics, operation records and follow-up information were recorded and analyzed. Among them, 34 patients had PTC concurrent with SHPT (PTC+SHPT) were enrolled. Control subjects were derived through 1:4 matching for age, sex and gender pathological subtype. 136 patients of papillary thyroid carcinoma were selected as control group after matching 1:4 for age, gender and pathological subtype.

**Results:** There were 34 patients coexisting with PTC+SHPT among the 531 surgery patients diagnosed as SHPT (6.4%). Mean tumor diameter of PTC+SHPT group was smaller than that in PTC group (5.57mm vs 9.00mm,  $p=0.001$ ). The proportion of papillary thyroid micro-carcinoma in PTC+SHPT group were significantly higher than that in PTC group [29 (85.29%) vs 86 (63.24%),  $P=0.014$ ]. There were no statistically significant difference among the tumor multicentricity [15 (44.12%) vs 39 (28.68%),  $P=0.066$ ], tumor bilaterality [9(26.47%) vs 29(21.32%),  $P=0.499$ ] tumor extrathyroidal extension [2(5.88%) vs 19 (13.97%),  $P=0.255$ ] and lymph node metastasizes rate [12 (35.29%) vs 49 (36.03%),  $P=1.000$ ]. We found differences between PTC+SHPT group and PTC group patients with respect to contralateral thyroidectomy [10 (29.41%) vs 70(51.47%),  $P=0.023$ ] and lymph node dissection [22 (64.71%) vs 125(91.91%),  $P=0.001$ ]. There was no significant difference between PTC+SHPT group and PTC group in prognostic staging [33 (97.06%) vs 122 (89.71%),  $P=0.309$ ] and recurrence [mean follow-up time 36 months vs 39 months,  $P=0.33$ ].

**Conclusions:** The prevalence of PTC is high in patients with SHPT. Compared with PTC in the general population, most of PTC with SHPT are occult thyroid carcinoma and present no significant difference in tumor pathological features and prognostic staging. It is necessary for surgeons to make more adequate preoperative prediction and do more careful examination during the surgery in case of missing the coexistence of PTC in SHPT patients.

## Background

Secondary hyperparathyroidism (SHPT), as a common complication of end-stage renal disease (ESRD), might develop ultimately in nearly all patients with chronic kidney disease [1, 2]. It is responsible for bone pain, itching, mineral bone disorders and the progression of ESRD, associated with a high risk of

cardiovascular events and death[3, 4]. Some SHPT patients at early stage can be treated with drugs such as Lanthanum carbonate and Cinacalcet, while others need surgical intervention because of drugs ineffectiveness[5–7]. With the progress of the disease, surgical intervention is required for SHPT when drug therapy become ineffective or parathyroid hormone (PTH) levels over a certain range.

However, it remains unclear whether secondary hyperparathyroidism accounts for more invasive papillary thyroid carcinoma (PTC) in terms of morbidity, tumor pathological characteristics and prognosis. The aim of this study was to evaluate the rate and tumor characteristics of PTC in patients of SHPT.

As the most common thyroid carcinoma (TC), PTC usually presents a indolent tumor biological behavior high incidence and low mortality[8, 9]. It has been reported that the high incidence of thyroid carcinoma in ESRD patients[10], led to growing interest in investigation of the impact of SHPT on TC in terms of occurrence and tumor biological behavior. However, it remains unclear whether secondary hyperparathyroidism accounts for more invasive PTC in terms of morbidity, tumor pathological characteristics and prognosis. The aim of this study was to evaluate the rate and tumor characteristics of PTC in patients of SHPT.

## Methods

### Patients and methods

A total of 531 patients diagnosed of SHPT and underwent surgery were evaluated retrospectively from January 2013 to December 2018 in the first affiliated hospital of the Zhejiang University. Patients' demographics, operation records and follow-up information were recorded and analyzed. Patients with primary hyperparathyroidism (PHPT), tertiary hyperparathyroidism or multiple endocrine neoplasm were excluded. Among them, 34 patients had PTC concurrent with SHPT (PTC + SHPT) were enrolled. Control subjects were derived through 1:4 matching for age, sex and gender pathological subtype. 136 patients of papillary thyroid carcinoma were selected as control group after matching 1:4 for age, gender and pathological subtype. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University.

### Surgical indication and approach

The 34 patients with PTC + SHPT were surgically treated by the recommendation of the latest guidelines of Kidney Disease: Improving Global Outcomes[11]. Among them, 33 patients underwent total parathyroidectomy with auto-transplantation and 1 patient underwent subtotal parathyroidectomy. Of the 136 patients with PTC, thyroidectomy indications and surgical procedures followed the latest guidelines for PTC of American Thyroid Association[12]. Total thyroidectomy was performed in patients with bilateral tumors, multiple tumors, abnormal lymph nodes, or extrathyroidal extension in the light of preoperative examination or intraoperative evaluation. Central neck dissection (CND) included removal of all nodes and fibro-fatty tissue extending vertically from the hyoid bone to the thoracic inlet and laterally  
tid artery to the midline of the trachea. Therapeutic CND was

conducted if abnormal lymph node (LN) were detected in preoperative or intraoperative examination; Prophylactic CND was considered in tumors with T stage of T3 and T4. Lateral neck dissection (LND), include modified radical neck dissection and selective neck dissection, was performed when lateral LN metastasis was confirmed preoperatively[13].

## Statistical analysis

Statistical analysis was performed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics for continuous variables was expressed as mean  $\pm$  standard deviation, and for non-normally distributed variables was expressed as median (min-max). Bivariate analysis was conducted with independent sample t-test, comparing means. Categorical variables were expressed in number and percentage (%), and Fisher's chi-square test was used to assess the differences between groups with regard to the categorical variables. A value of  $P < 0.05$  was considered statistically significant.

## Results

### *PTC+SHPT screening process*

All 531 SHPT patients underwent parathyroidectomy and 168 of them also underwent thyroidectomy. According to pathological diagnosis of the removed thyroid tissue, they were divided into three sub-groups: patients with normal thyroid tissue, patients with benign thyroid nodules and patients with thyroid carcinoma. The reasons for thyroidectomy in each group were as follows: The first sub-group was normal thyroid tissue which was 34 cases (Fig. 1). The reason for the resection were as follows: 9 of them is for the abnormal anatomy of the thyroid glands obstructed resecting parathyroid gland (PG); 18 of them were mistaken for PG; and another 7 of them were a small piece of thyroid tissue attached to the resected PG. The second subgroup was 100 cases of benign thyroid nodules. The reason for the resection were as follows: 41 of them is for the anatomy of the thyroid glands obstructed resecting PG; 8 of them were mistaken for PG; and the other 51 cases were for their reasons (such as tumor diameter  $> 4$ cm, multiple thyroid nodules, patients' intentions). The third sub-group was TC in 34 cases, all of which were proved to be PTC pathologically. The incidence of PTC in the group of SHPT patients who needs surgery was 6.4% (34/531). Among them, 17 cases were suspected cancer preoperatively by ultrasound. However, another 17 cases who were not suspected malignant preoperatively were PTC by intra-operative frozen section or post-operative pathology.

### *clinical characteristics of PTC+SHPT Patients*

In the 34 PTC + SHPT patients, 15 were male and the average age was 47 years old. All of them were chronic kidney disease stage 5 combined with SHPT. The average pre-operative parathyroid hormone level was 2010 pg/ml, and the average post-operative hormone level was 24 pg/ml (Table 1).

### *Comparison of tumor characteristics of PTC+SHPT group and PTC group*

The comparison of tumor characteristic between PTC+SHPT group and PTC group is shown in Table 2. Mean tumor diameter of PTC+SHPT group was smaller than that in PTC group (5.57mm vs 9.00mm,  $p=0.001$ ). Most of them are papillary thyroid microcarcinoma (PTMC), and the proportion of PTMC in PTC+SHPT group were significantly higher than that in PTC group [29 (85.29%) vs 86 (63.24%),  $P=0.014$ ]. However there was no statistical significance in tumor multicentricity [15 (44.12%) vs 39 (28.68%),  $P=0.066$ ], tumor bilaterality [9(26.47%) vs 29(21.32%),  $P=0.499$ ], tumor extrathyroidal extension [2 (5.88%) vs 19 (13.97%),  $P=0.255$ ] and lymph node metastasizes rate [12 (35.29%) vs 49 (36.03%),  $P=1.000$ ].

#### *Comparison of surgical approach of PTC+SHPT group and PTC group*

The comparison of surgical approach between PTC+SHPT group and PTC group is shown in Table 3. Contralateral thyroidectomy, including contralateral partial thyroidectomy, contralateral subtotal thyroidectomy and contralateral total thyroidectomy; Lymph node dissection, including CND and LND. The percent of contralateral thyroidectomy [10 (29.41%) vs 70 (51.47%),  $P=0.023$ ] and lymph node dissection [22 (64.71%) vs 125 (91.91%),  $P=0.001$ ] during surgery in PTC+SHPT group were significantly lower than that in PTC group.

#### *Prognostic staging and survival of PTC+SHPT group and PTC group*

All PTC patients in our study were stage I or II, as shown in Table 4. There was no statistical significance of prognostic staging between PTC+SHPT group and PTC group [33(97.06%) vs 122(89.71%),  $P=0.309$ ]. The mean follow-up time of 34 patients with PTC+SHPT was 36 months. Among them, one case was lost to follow-up, 1 case died of heart failure, and 32 cases had no recurrence by the end of the follow-up. The mean follow-up time of 136 patients with PTC was 39 months. Among them, 1 case was lost to follow-up, 0 case died, 3 cases relapsed and 132 cases had no recurrence by the end of the follow-up. The disease-free survival of two groups are shown in Fig.2,  $p=0.33$ .

## **Discussion**

Here, we analyzed 34 SHPT patients with pathologically proofed PTC from 531 SHPT patients underwent surgery to investigate whether SHPT accounts for more aggressive PTC in terms of morbidity, tumor pathological characteristics and prognosis.

According to previous research, several factors such as metabolic disorder of calcium, phosphorus, and vitamin D induced by SHPT, immunological incompetence accompanied by ESRD, and always aging are considered to be involved in the occurrence and development of thyroid dysfunction and PTC [14, 15]. Shih-Yi Lin et al found that ESRD patients with SHPT exhibited a 10.1-fold increased risk of thyroid carcinoma than ESRD patients without SHPT [16]. However in another study, 339 ESRD patients with SHPT and underwent surgical therapy were investigated and it showed that the incidence of PTC was 2.4% in SHPT group [17]. Compared with PTC detection rate in autopsy which ranged from 5–11%, they didn't find any significant correlation between PTC and SHPT. So, it is still under debate whether ESRD or

group of SHPT patients who needs surgery was 6.4%(34/531), far beyond the incidence of PTC in general population(0.5–6.9/100000), in China[18]. So we have reason to believe that SHPT is a risk factor for the PTC occurrence.

It has been reported with conclusion that PHPT may result in overdiagnosis of PTC and higher rates of tumor extrathyroidal extension and multicentricity in PHPT + PTC group, which indicates an associative etiology with more aggressive PTC [19][20]. However, there is hardly any research data analyzing the tumor characteristics of SHPT.

As previously proved, both gender and age are associated with the development of PTC[21]. The PTC + SHPT group contained 34 patients, 44.1% men and 55.9% women, whose average age was 47 years old. Then we matched the control group for age, gender and pathological subtype by 1:4. Ultimately, we found that compared with PTC group, PTC + SHPT group has smaller tumor diameter, which is the main characteristic of occult thyroid carcinoma. However, there were no statistically difference in tumor laterality (unilateral–bilateral), tumor multicentricity, tumor extra-thyroid extension, lymph node metastasis rate and prognostic staging. In the 34 patients of PTC + SHPT group, there were 12 (35.29%) with lymph node metastasis. Additionally, within the 29 patients of PTMC without SHPT, there were 9 patients (31.03%) with lymph node metastasis, in accord with previously reported data[13]. From the above results, we could not find any associative etiology of SHPT with more aggressive PTC in PTC + SHPT group. By contraries, the tumor characteristics of PTC in PTC + SHPT group was closer to occult PTC which was mostly composed of PTMC (85.29%). Reviewing the preoperative ultrasound and surgical records of 34 patients, we found that some patients were not suspected to have TC preoperatively, and received thyroidectomy just because of mistaking part of normal thyroid tissue of PG or TC during the surgery. These factors led to increased detection rate of occult thyroid carcinoma which tend to be smaller in diameter.

We found that when we were doing PTC surgery during parathyroidectomy, there was smaller chance of contralateral thyroidectomy or lymph node dissection. Combining the above data, we can see that it was mainly because the PTC in PTC + SHPT group often were occult PTC, presenting a more indolent tumor phenotype associated with minimal tissue trauma and maximal thyroid function retention. It has been proven previously that PTC, as an endocrine tumor, has good prognosis with very low mortality[22, 23]. Previous research showed that the relapse rate of PTC is about 1%-5%[24]. The follow-up data of the two groups in our research showed that there was no recurrence in PTC + SHPT group, but there were 3 recurrent patients in the PTC group. Due to the above prognosis data, we can conclude that SHPT is not a risk factor for the PTC recurrence. Based on our study, we can conclude that PTC has higher incidence in surgically treated patients of secondary hyperparathyroidism, and more often was occult PTC.

Nevertheless, this study had several limitations. The sample size of the study was limited, and the follow-up time was short. In that means, we need more prospective randomized controlled studies with larger sample size and longer follow-up time in the future to further prove the conclusions above.

## Conclusions

In conclusion, the prevalence of PTC is high in patients with SHPT, thus we must be alerted for the coexistence of PTC in surgery. Compared with PTC in the general population, most of PTC with SHPT are occult thyroid carcinoma and present no significant difference in tumor pathological features and prognostic staging. It is necessary for surgeons to make more adequate preoperative prediction and do more careful examination during the surgery in case of missing the coexistence of PTC in SHPT patients.

## List Of Abbreviations

PHPT primary hyperparathyroidism

PTC papillary thyroid carcinoma

TC thyroid carcinoma

SHPT secondary hyperparathyroidism

PTMC papillary thyroid microcarcinoma

PG parathyroid gland

ESRD end-stage renal disease

PTH parathyroid hormone

CND central neck dissection

LND lateral neck dissection

LN lymph node

PTX parathyroidectomy

## Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

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The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

#### Competing interests

The authors declare that they have no competing interests.

#### Funding

This study is supported by Grants from the National Natural Science Foundation of China (No. 81772853, 81972495, and 81902719), Grants from National Natural Science Foundation of Zhejiang (No. LY18H160012 and LQ18H120002), and the Key Project of Scientific and Technological Innovation of Zhejiang Province (No. 2015C03031).

#### Authors' contributions

Junhao Ma was a major contributor in writing the manuscript, collecting and analyzing data; Zhuochao Mao was a major contributor in collecting and analyzing data; Haohao Wang, Yimin Lu, Jun Yang contributed to designing research, performing research and analyzing data; Weibin Wang revised the paper and analyzed the data; Lisong Teng and Weibin Wang developed the idea for the study and revised the paper. All authors read and approved the final manuscript.

#### Acknowledgements

Not applicable.

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## Tables

**Table 1 Basic information of PTC+SHPT group**

	PTC+SHPT(n=34)
Male	15(44.1%)
Age*(years)	47(30-69)
Serum iPTH pre-operative* (pg/ml)	2010(203-4133)
Serum iPTH pro-operative* (pg/ml)	24(3-392)

Abbreviations: PTC, papillary thyroid carcinoma; SHPT, Secondary hyperparathyroidism.

\* Median(min-max)

**Table 2 Comparison of tumor characteristics of PTC+SHPT group and PTC group**

	PTC+SHPT (n = 34)	PTC (n = 136)	P
Age*(years)	47(30-69)	47(30-69)	1.000
Male	15(44.1%)	15(44.1%)	1.000
Tumor diameter*(mm)	5.57(0.5-15)	9.00(0.5-40)	<b>0.001</b>
Tumor diameter <10mm	29(85.29%)	86(63.24%)	<b>0.014</b>
Tumor bilaterality	9(26.47%)	29(21.32%)	0.499
Tumor multicentricity	15(44.12%)	39(28.68%)	0.066
Tumor extrathyroidal extension	2(5.88%)	19(13.97%)	0.255
Lymph node metastasis rate	12(35.29%)	49(36.03%)	1.000

Abbreviations: PTC, papillary thyroid carcinoma; SHPT, Secondary hyperparathyroidism.

$P \leq 0.05$  was considered statistically significant.

\*Average(min-max)

**Table 3 Comparison of surgical approach of PTC+SHPT group and PTC group**

	PTC+SHPT (n = 34)	PTC (n = 136)	P
Contralateral thyroidectomy	10(29.41%)	70(51.47%)	<b>0.023</b>
Lymph node dissection	22(64.71%)	125(91.91%)	<b>0.001</b>

Abbreviations: PTC, papillary thyroid carcinoma; SHPT, Secondary hyperparathyroidism.

$P \leq 0.05$  was considered statistically significant.

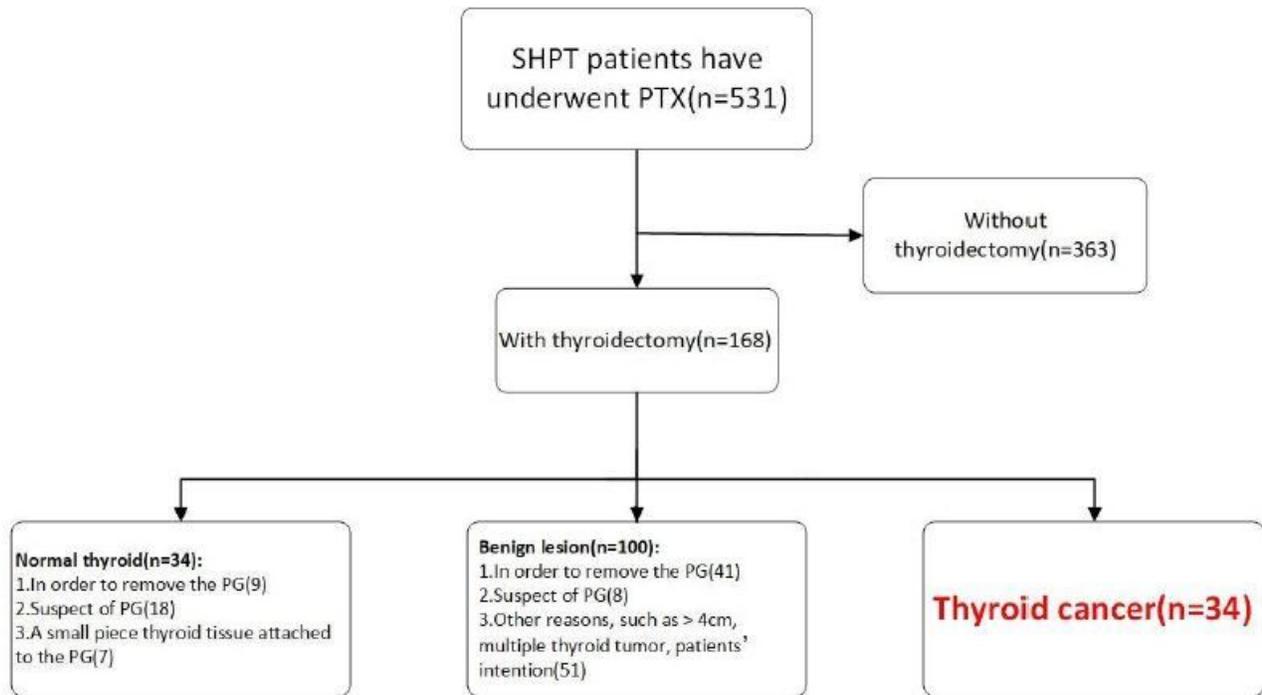
**Table 4 Comparison of prognostic staging of PTC+SHPT group and PTC group**

Prognostic staging	PTC+SHPT (n = 34)	PTC (n = 136)	P
I	33(97.06%)	122(89.71%)	0.309
II	1(2.94%)	14(10.29%)	0.309

Abbreviations: PTC, papillary thyroid carcinoma; SHPT, Secondary hyperparathyroidism.

$P \leq 0.05$  was considered statistically significant.

## Figures



Abbreviations: PTC, papillary thyroid carcinoma; SHPT, Secondary hyperparathyroidism; PTX, parathyroidectomy; PG, parathyroid gland.

Figure 1

Screening process of PTC+SHPT among SHPT patients

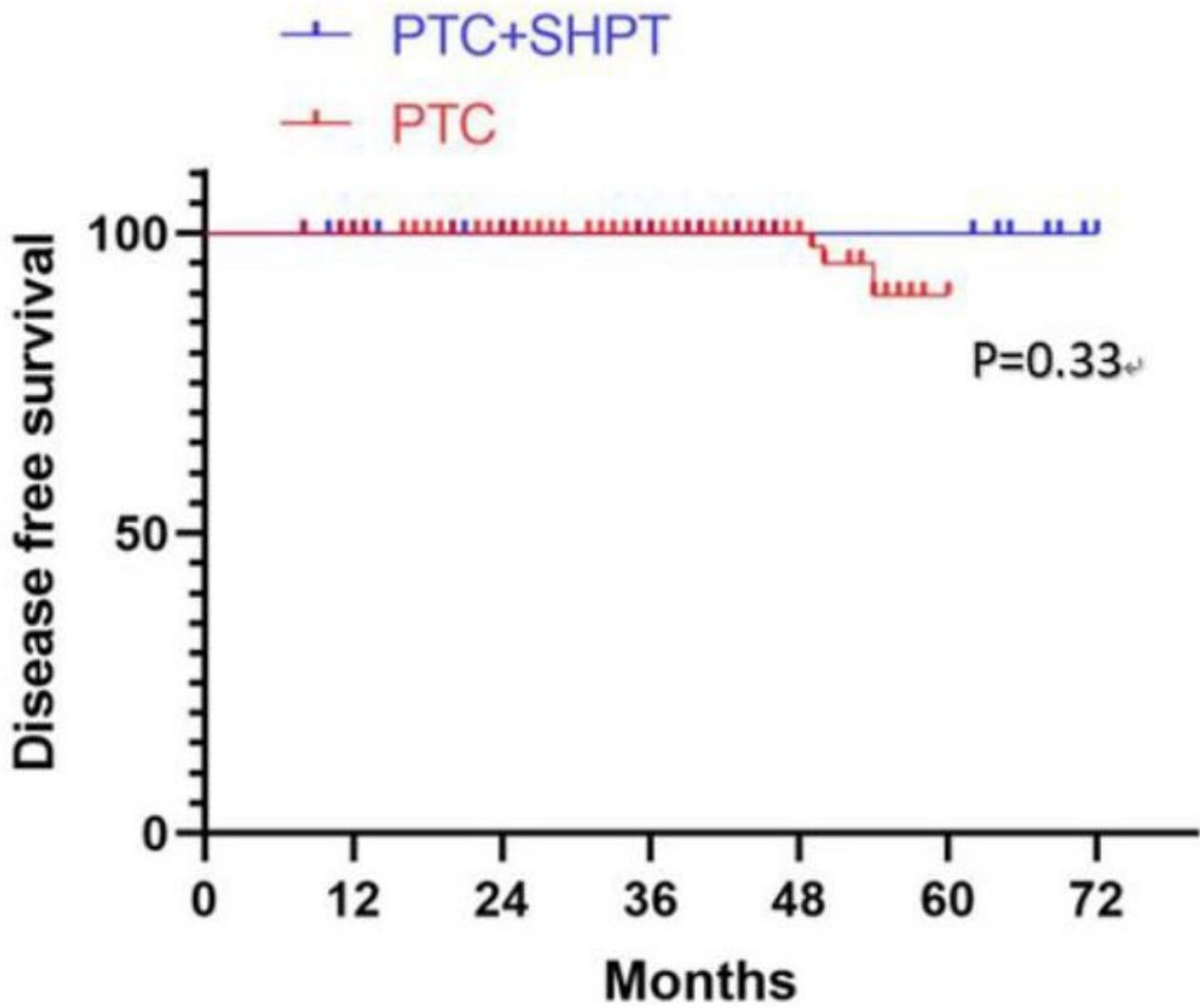


Figure 2

Disease free survival of PTC+SHPT group and PTC group