A Retrospective Case-control Study of Tumor Characteristics of Coexistent Papillary Thyroid Carcinoma Diagnosed in Surgically Treated Patients for Secondary Hyperparathyroidism: Higher Incidence and More Often Occult Papillary Thyroid Carcinoma

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Research

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

Posted Date: November 20th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-111304/v1

Abstract

Background :Coexistence of primary hyperparathyroidism (PHPT) and PTC is common and may be associative with more aggressive papillary thyroid carcinoma (PTC) for higher rates of extrathyroidal extension and multicentricity. However, it remains unclear whether secondary hyperparathyroidism (SHPT) 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 operated for secondary hyperparathyroidism (SHPT).

Methods:A total of 531 patients with PTC who underwent surgery were evaluated retrospectively from January 2013 to December 2018 in the first affiliated hospital of the Zhejiang University. Patient demographics, operative and postoperative outcomes were recorded and analyzed. Among them, 34 patients of co-occurrence of secondary hyperparathyroidism and papillary thyroid carcinoma (PTC+SHPT) were enrolled. Control subjects were derived through 1:4 matching for age, sex and gender pathological subtype. 34 patients of co-occurrence of secondary hyperparathyroidism and papillary thyroid carcinoma (PTC+SHPT) were selected as control group after matching 1:4 for age, gender and pathological subtype.

Results:There were 34 patienst coexisting with PTC+SHPT among the 531 surgery patients of SHPT(6.4%). Mean tumor diameter of group PTC+SHPT was smaller than that in group PTC (5.57mm vs 9.00mm, p=0.000). The proportion of papillary thyroid microcarcinoma(PTMC means PTC with a diameter smaller than 10 mm) in group PTC+SHPT were significantly higher than that in group PTC [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 bilaterally [9(26.47%) vs29(21.32%), P=0.499] tumor extrathyroidal extension [2(5.88%) vs19 (13.97%), P=0.255] and lymph node metastasises rate [12 (35.29%) vs 49 (36.03%), P=1.000]. We found differences between group PTC+SHPT and group PTC 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=0.000].There was no significant difference between group PTC+SHPT and group PTC 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 higher in patients with SHPT than in the general population. Compared with PTC in the general population, most of PTC with SHPT are occult thyroid carcinoma and present no significant difference in tumor multicentricity, tumor bilaterally,tumor extrathyroidal extension, lymph node metastasises and prognostic staging. It's 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, though there were no accurate date[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 or resisitance[5–7]. It has been reported that the high incidence of TC in ESRD patients[8], 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 there is any difference of morbidity, tumor pathological characteristics and prognosis between the PTC patients with or without SHPT. Therefore, we conducted the retrospective study to explore the clinical and pathological characteristics of patients with PTC + SHPT.

Methods

Patients and methods

A total of 531 surgically treated SHPT patients were reviewed and analyzed retrospectively in the first affiliated hospital of the Zhejiang University from January 2013 to December 2018. Patients with PHPT, tertiary hyperparathyroidism or multiple endocrine neoplasm were excluded. Among them, 34 patients of SHPT combined with TC were enrolled. The pathological diagnoses were all PTC. Control subjects were derived through 1:4 matching for age, gender and pathological subtype. Matched 136 patient were all initially treated in our hospital with simple TC resection without a history of thyroid or neck sugery and irradiation. The study protocol was approved by the Ethics Committee of the First Addiliated Hospital of Zhejiang University.

Surgical approach

Of the 34 patients with PTC + SHPT, 33 patients underwent total parathyroidectomy with auto-transplantation(TPTX + AT) and 1 patient underwent subtotal parathyroidectomy(SPTX). Surgical procedures followed the latest guidelines for PTC of National Comprehensive Cancer Network(NCCN) [9]. Total thyroidectomy was performed in patients with bilateral tumors, multiple tumors, abnormal lymph nodes, or extrathytoidal extension(ETE) 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 from the medial border of the common carotid artery to the midline of the trachea. Therapeutic CND was selected when detecting an abnormal lymph node(LN) based on preoperative or intraoperative examination; Prophylactic CND was considered in the case of advanced primary tumors(T3/T4) of according to the surgeon’s personal preference intraoperative. Lateral neck dissection(LND), comprised modified radical neck dissection and selective neck dissection, was performed when lateral LN metastasis was confirmed preoperatively[10].

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 ± standard deviation(SD), 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 percent(%), and Fisher's chi-squuare 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

Among the 531 SHPT patients who underwent parathyroidectomy from January 2013 to December 2018, 168 cases were removed thyroid tissue simultaneously during the surgery. According to pathological diagnosis of the removed thyroid tissue, they were divided into three sub-groups: 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 ther 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 diagnodsed PTC by intra-operative frozen section or post-operative pathology.

PTC + SHPT Patients' relavent clinical characteristics

Of the 34 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).

Table 1
Basic information of group PTC + SHPT

	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)	

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

The comparison of tumor characteristic between group PTC + SHPT and group PTC is shown in Table 2. Mean tumor diameter of group PTC + SHPT was smaller than that in group PTC (5.57 mm vs 9.00 mm, p = 0.000). Most of them are papillary thyroid microcarcinoma (PTMC), and the proportion of PTMC in group PTC + SHPT were significantly higher than that in group PTC [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 bilaterally [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 metastasises rate [12 (35.29%) vs 49 (36.03%), P = 1.000].

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

	PTC + SHPT (n = 34)	PTC (n = 136)	P
Age*(years)	47(30–69)	47(30–69)	1
Male	15(44.1%)	15(44.1%)	1
Tumor diameter*(mm)	5.57(0.5–15)	9.00(0.5–40)	0.000
Tumor diameter < 10 mm	29(85.29%)	86(63.24%)	0.014
Tumor bilaterally	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 ≤ 0.05 was considered statistically significant.			
*Average(min-max)			

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

The comparison of surgical approach between group PTC + SHPT and group PTC 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 = 0.000] during surgery in group PTC + SHPT were significantly lower than that in group PTC.

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

	PTC + SHPT (n = 34)	PTC (n = 136)	P
Contralateral thyroidectomy	10(29.41%)	70(51.47%)	0.023
Lymph node dissection	22(64.71%)	125(91.91%)	0.000
Abbreviations:PTC, papillary thyroid carcinoma;SHPT, Secondary hyperparathyroidism.			
P ≤ 0.05 was considered statistically significant.			

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

All PTC in our study were prognostic staging□or □, shown in Table 4. There was no statistical significance of prognostic staging between group PTC + SHPT and group PTC[33(97.06%) vs122(89.71%), P = 0.309]. The mean follow-up time of 34 patients with PTC + SHPT was 36 months. Among them, 1 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.

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

Prognostic staging	PTC + SHPT (n = 34)	PTC (n = 136)	P
□	33(97.06%)	122(89.71%)	0.309
□	1(2.94%)	14(10.29%)	0.309
Abbreviations:PTC, papillary thyroid carcinoma;SHPT, Secondary hyperparathyroidism.			
P ≤ 0.05 was considered statistically significant.			

Discussion

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

From 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 dysfuction and PTC [11, 12]. Shih-Yi Lin et al found that ESRD patients with SHPT exhibited a 10.1-fold increased risk of thyroid carcinoma than did ESRD patients without SHPT [13]. However there is a surgery population-based cohort study conducted with 339 ESRD with SHPT patients in Germany which showed that the incidence of PTC was 2.4% in the group SHPT[14]. Compared with PTC detection rate in European autopsy studies ranged from 6–9% after reviewed literature, they didn't find any significant correlation between PTC and SHPT. So, it is still under debate whether ESRD or SHPT can induce higher incidence rate of PTC. Here, our study showed that the incidence of PTC in the 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[15]. 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 the group PHPT + PTC, which indicates an associative etiology with more aggressive PTC [16],[17]. 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[18]. The group PTC + SHPT 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 group PTC, group PTC + SHPT 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 extrathytoidal extension, lymph node metastasis rate and prognostic staging. In group PTC + SHPT, there were 12 patients(35.29%) with lymph node metastasis. Among them, there were 9 patients (31.03%) with lymph node metastasis within the 29 patients of PTMC, same rate as previously reported data in PTMC without SHPT[10]. In addition, there were 3 patients with lymph node metastasis in 5 with tumor diameter greater than 1 cm. From the above results, we could not find any associative etiology of SHPT with more aggressive PTC in group PTC + SHPT. By contraries, the tumor characteristics of PTC in group PTC + SHPT was closer to occult PTC which was mostly composed of PTMC (85.29%). Reviewing the preoperative B-mode ultrasound and surgical records of 34 patients, we found that some partients 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 group PTC + SHPT often were occult PTC, presenting a more indolent tumor phenotype associated with minimal tissue trauma and maximal function retention. It has been proven previously that PTC,as an endocrine tumor, has good prognosis with very low mortality[19, 20]. Previous research showed that the relapse rate of PTC is about 1%-5%[21]. The follow-up data of the two groups in our research showed that there was no recurrence in group PTC + SHPT, but there was 3 recurrent patients in the group of PTC. 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 really limited, and the follow-up time was short. In that means, we need more prospective randomized controlled studies with larger samle size and longer follow-up time in the future to further prove the conclusions above.

Conclusions

In conclusion, we can believe that the prevalence of PTC is higher in patients with SHPT than in the general population that we must be alerted for the coexistence of PTC when doing the SHPT surgery. Compared with PTC, most of PTC in SHPT are occult thyroid carcinoma and present no significant difference in tumor multicentricity, tumor bilaterally,tumor extrathyroidal extension, lymph node metastasises and prognostic staging. Therefore, we suggest the surgeon to do more adequate preoperative predictors and careful examination during the operation in SHPT patients, for fear of missing of PTC.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed 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 research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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 revisioned the paper and analyzed the data; Lisong Teng developed the idea for the study and revisioned the paper. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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Figures

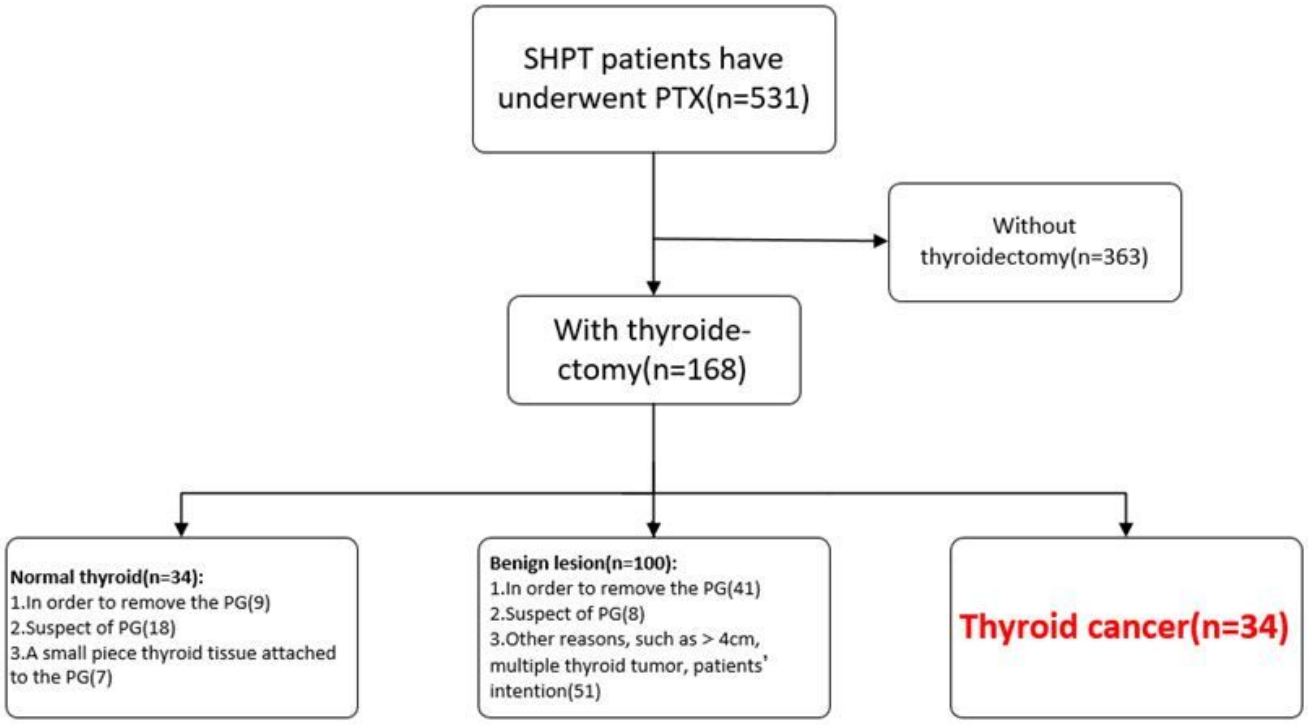
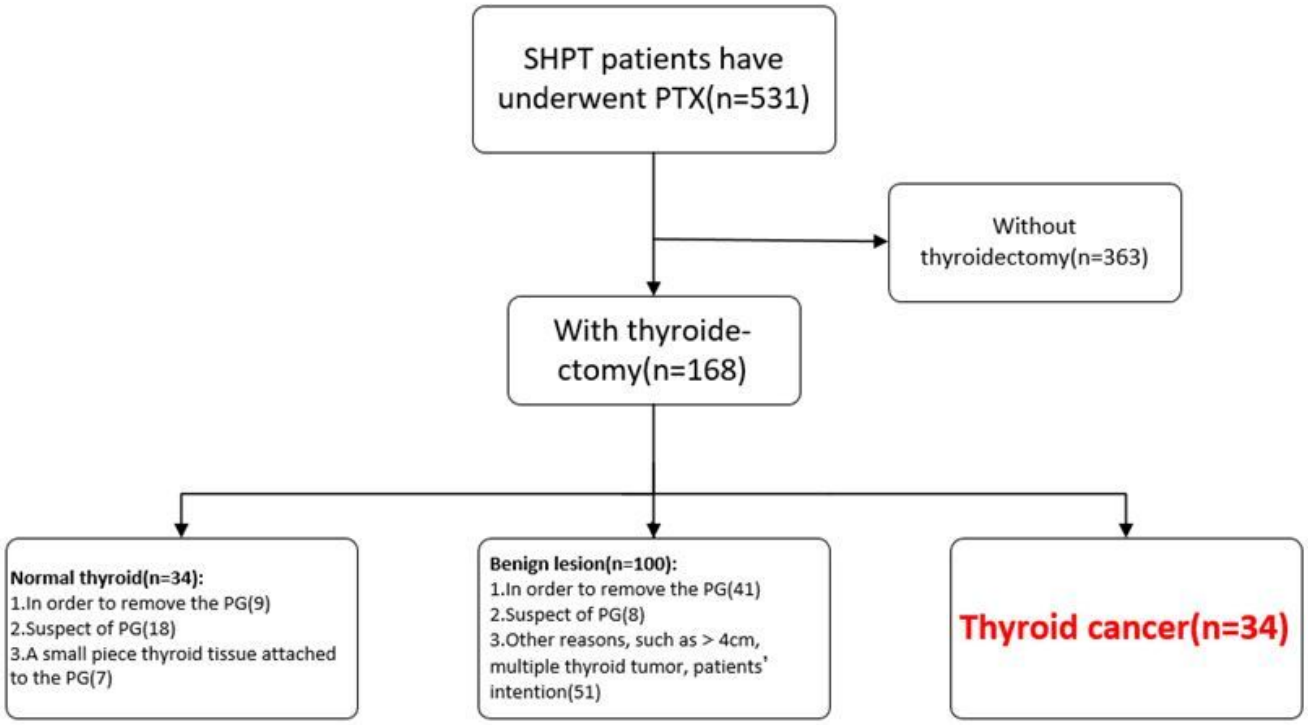


Figure 1

Screening process of PTC+SHPT among SHPT patients



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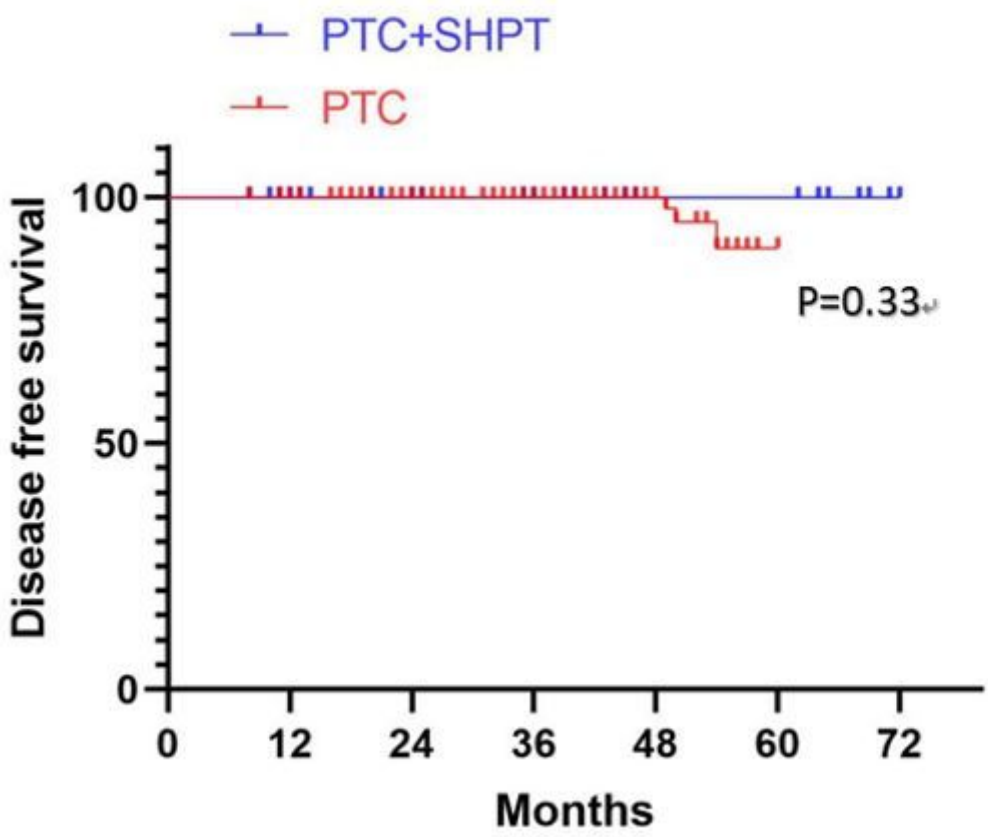
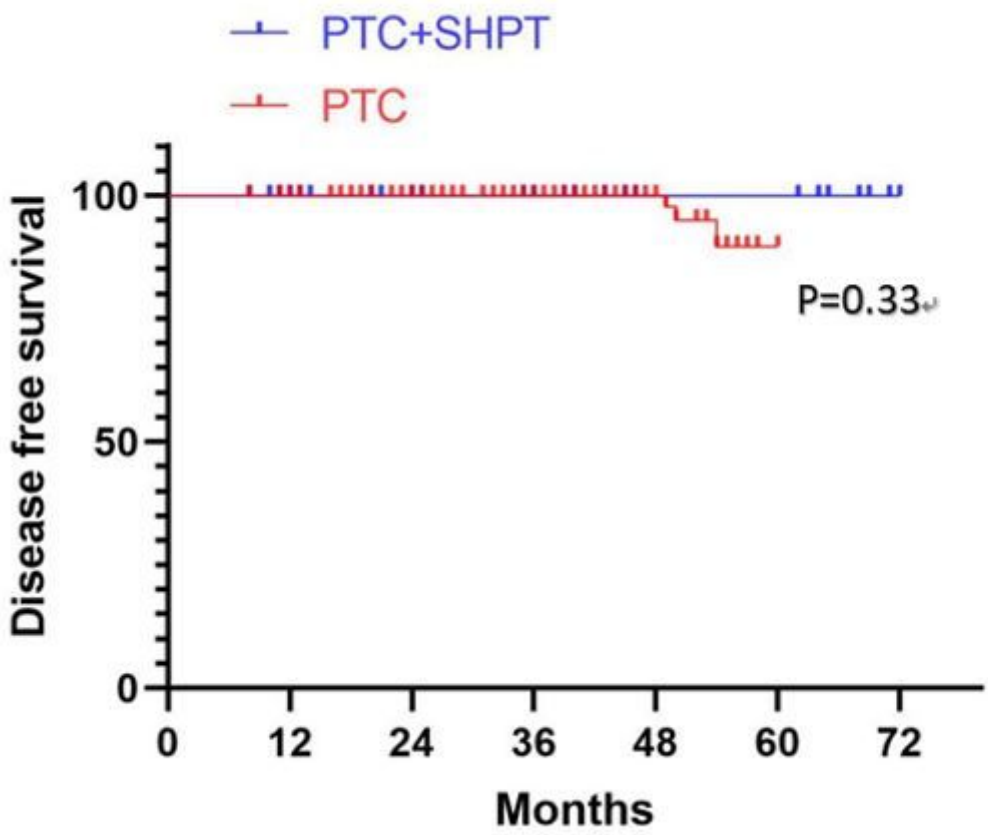


Figure 2

Disease free survival of group PTC+SHPT and group PTC



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