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Original Research

The role of thymus preservation in parathyroid gland function and surgical completeness after bilateral central lymph node dissection for papillary thyroid cancer: A randomized controlled study

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ABSTRACT

Background: The clinical value of thymus preservation during thyroid carcinoma surgery remains unclear. The aim of this study is to explore the role of bilateral thymus preservation in parathyroid glands (PGs) function and surgical completeness in total thyroidectomy (TT) with bilateral central lymph node dissection (CLND).

Materials and methods: Fifty-four consecutive patients who underwent TT and bilateral CLND were assigned to the thymus preservation (TP) group (n = 27) and the bilateral thymectomy (BT) group (n = 27). Surgical completeness was evaluated by the number of lymph nodes dissected, serum Tg level and ultrasound findings postoperatively.

Results: Incidental parathyroidectomy was more common in the BT group (29.6% vs 7.4%, p = 0.038). Patients in the BT group had higher risks of neuromuscular symptoms (63.0% vs 29.6%, P = 0.014) and transient hypoparathyroidism (70.4% vs 25.9%, P = 0.001). The incidence of persistent hypoparathyroidism failed to show a significant difference between the TP and BT groups (0 vs 14.8%, P = 0.111). However, those with transient hypoparathyroidism in the BT group had a lower level of serum PTH at 3 weeks postoperatively (p = 0.001). There was no significant difference in the number of lymph nodes dissected (5.89 ± 3.12 vs 8.56 ± 6.93, P = 0.077) and preablation sTg level (1.82 ± 2.18 vs 1.42 ± 1.56 ng/ml, P = 0.775) between the TP and BT groups. No metastatic lymph nodes were found on sonography at 3 months postoperatively in both groups. Conclusion: Thymus preservation had benefits on protecting PGs and promoting rapid clinical resolution of hypoparathyroidism. It had no effects on oncologic completeness of TT with bilateral CLND.

1. Introduction

Among all neck compartments, the ipsilateral central neck compartment is involved most frequently in lymph node metastasis of papillary thyroid carcinoma (PTC) [1]. Even for cN0 PTCs, lymph node metastases are found in 40–60% of the central lymph nodes after surgery [2]. There is consensus on performing central lymph node dissection (CLND) in patients with clinical lymph node metastases. However, for patients without evidence of lymph node metastases before surgery, prophylactic neck dissection remains controversial due to the lack of clear data regarding its survival benefit and complications [3]. Hypoparathyroidism is a major complication when it comes to CLND, which closely correlates with the extent of operation as well as incidental removal of parathyroid glands (PGs) [4,5].

Boundaries for central neck dissection are defined superiorly by the hyoid bone, inferiorly by the suprasternal notch, laterally by the medial aspect of the carotid sheath, posteriorly by the prevertebral fascia, and anteriorly by the superficial layer of the deep cervical fascia according to the 2015 America Thyroid Association (ATA) consensus statement [6]. The upper poles of the thymus as well as the inferior PGs are included in the boundaries.

The thymus and the inferior PGs are both derived from the endoderm of pharyngeal pouch III [7] and are located in close proximity to each other within the paratracheal area of the central neck compartment. They share the same blood supply [8]. Thymus preservation during CLND may reduce the risk of PG blood supply injuries or incidental removal of the PGs, and thus decrease the prevalence of postoperative hypocalcemia. However, the potential risk of thymic

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metastasis makes thymus preservation controversial, despite of its low incidence in PTC [9]. Therefore, it is necessary to weigh the benefits against the risks of thymus preservation and determine the optimal extent of CLND.

Previous retrospective observational studies have been performed comparing bilateral and unilateral thymectomy (upper poles) during CLND for unilateral differentiated thyroid cancer [10,11]. However, a lack of prospective randomized controlled trials has hampered the current understanding on the benefits and risks of thymus resection or preservation. With regards to patients with bilateral PTC, whether bilateral thymectomy or thymus preservation during bilateral CLND is the problem that needs to be addressed. In this prospective, randomized study, we aimed to compare the outcomes of thymus preservation with bilateral thymectomy in order to determine the proper extent of CLND for bilateral PTC.

2. Materials and methods

The study protocol was approved by our institutional Ethics Committee and written informed consent was obtained from each participant. This study was registered on the Chinese Clinical Trial Registry (ChiCTR) database and the unique identifying number has been listed on the title page. The whole work has been reported in line with Consolidated Standards of Reporting Trials (CONSORT) Guidelines.

2.1. Patients

Patients satisfying the following criteria were recruited: (1) age 18–70 years; (2) preoperatively highly suspected with bilateral papillary carcinoma based on ultrasound findings or ultrasound -guided fine needle aspiration cytology; (3) signed informed consent. Patients were excluded if they met one or more of the following criteria: (1) contraindications for anesthesia such as pregnancy, multiple organ failure, or mental disease; (2) a history of neck surgery or radiotherapy; (3) concomitant Graves disease; (4) preoperative diagnosis of lateral lymph node metastases based on ultrasound, computed tomography, or fine needle aspiration cytology; (5) preoperative hypoparathyroidism or hypocalcemia; and (6) thymus disease. Between November 2016 and November 2017, 54 consecutive PTC patients were randomly allocated to either the TP group (thymus preservation) or the BT group (bilateral thymectomy).

2.2. Randomization

The randomized sequence was generated by a statistician who was not involved in this study. Block randomization was performed using SAS 9.4 (SAS, Cary, NC, USA). Randomization took place in the operating room by the sealed envelope method, after total thyroidectomy (TT) and frozen section examination. If the frozen section examination turned out not to be bilateral PTC, the patient was excluded from the trial. All patients were operated by the same surgery team and blinded to the interventions.

2.3. Surgical techniques

Routine central neck dissection (level VI) was performed in the regions included superiorly by the hyoid bone, inferiorly by the suprasternal notch, laterally by the medial aspect of the carotid sheath, posteriorly by the prevertebral fascia, and anteriorly by the superficial layer of the deep cervical fascia according to the 2015 America Thyroid Association consensus statement [6]. The bilateral thymus glands were preserved *in situ* in the TP group while the upper poles of the bilateral thymus were resected along with thyrothymic ligament in the BT group. The PGs and recurrent laryngeal nerve were identified and protected during dissection in both groups. PG autotransplantation were performed if glands appeared to be devascularized completely.

2.4. Outcome measures

"Hypoparathyroidism" was defined as a condition in which calcium or vitamin D supplementation was required to maintain normocalcemia and serum intact parathyroid hormone (PTH) concentration was less than 15 pg/ml (range 15–65 pg/mL). Lack of recovery of PTH level to the normal range within 6 months was defined as "permanent hypoparathyroidism; " otherwise, it was defined as "transient hypoparathyroidism." The decreased ratio of PTH was calculated as: (preoperative PTH-postoperative PTH) × 100/preoperative PTH.

Primary outcome measures were function of parathyroid gland (e.g. incidence of transient and persistent hypoparathyroidism) and surgical completeness (e.g. number of lymph nodes dissected, thyroglobulin (Tg) and ultrasound findings). The secondary end points were operative duration, hospitalization time and complications (e.g. Vocal cord palsy).

2.5. Perioperative management and follow-up

All patients underwent preoperative ultrasound, fine needle aspiration biopsy, and direct laryngoscopy which aimed to assess vocal cord motility. Postoperative evaluation of all patients included assessments of PTH levels and pathological characteristics (e.g., incidental removed PGs).

The normal range of PTH levels was 15–65 pg/ml. Patients with a serum calcium of less than 1.90 mmol/L and symptoms of hypocalcemia (e.g., paresthesia, tetany) took oral calcium carbonate, vitamin D3 chewable tablets (1.2–2.4 g/day), and calcium gluconate (3.6 g/day).

Postoperative follow-up was performed by outpatient visits, telephone interview, and written correspondence. Patients were clinically evaluated, including measurements of neuromuscular symptoms, as well as serum calcium and PTH levels, which were measured on 3 weeks, 3 months and 6 months postoperatively. Moreover, evaluations of serum calcium and PTH levels were no longer needed when these indexes reverted to normal. Thyroid stimulating hormone suppression with thyroxine therapy was given to all patients after surgery. Thyroid function test, Tg and TgAb levels were checked on postoperative week 3. Neck ultrasound was performed at 3 months after surgery. For patients with the indications for radioactive iodine (RAI) treatment, T4 was withdrawn for 4 weeks before ablation. Preablation stimulated thyroglobulin (sTg) was measured one day before RAI treatment. Successful ablation was assumed when a serum Tg level of less than 1.0 ng/mL was achieved.

2.6. Statistical analysis

Sample size calculation was based on the transient hypocalcemia data reported by El et al. (52.4% in bilateral thymectomy vs. 13.7% in unilateral thymectomy) using PASS 15.0 (NCSS, Kaysville, UT) [10]. Since 22 patients per group were required (for an alpha value of 0.05 and power of 80%), we aimed for a total of 54 patients, considering a 20% dropout rate. Baseline and follow-up information were calculated by an independent researcher. The database was exported to SPSS software (version 19.0; IBM-SPSS, Inc., Chicago, IL, USA). Quantitative data accord with normal distribution, with mean ± standard deviation, were analyzed by *t*-test. Mann-Whitney Test was applied for those dissatisfied with normal distribution. Categorical variables were compared between groups using Pearson's chi-squared or Fisher's exact test.

3. Results

Together, 27 patients who underwent thymus preservation were allocated in the TP Group and 27 patients who underwent bilateral

Table 1
Clinical and histological characteristics of patients in the TP group and BT group.

	TP group (n = 27)	BT group (n = 27)	P value
Age (years)	45.37 ± 7.85	47.33 ± 11.61	0.470
Gender			
Male (N, %)	5 (18.5)	6 (22.2)	0.735
Female (N, %)	22 (81.5)	21 (77.8)	
BMI (kg/m2)	24.67 ± 4.06	25.27 ± 3.19	0.548
Tumor size			
Mean (mm)	9.78 ± 6.49	8.85 ± 4.92	0.557
< 10 mm (N, %)	13 (48.1)	15 (55.6)	0.586
≥10 mm (N, %)	14 (51.9)	12 (44.4)	
Extracapsular invasion (N, %)	3 (11.1)	4 (14.8)	> 0.999
Multifocality			
2 foci (N, %)	17 (63.0)	21 (77.8)	0.233
≥3 foci (N, %)	10 (37.0)	6 (22.2)	
Operative duration (min)	129.52 ± 31.73	121.30 ± 33.10	0.356
Hospitalization time (day)	6.22 ± 1.97	6.93 ± 2.17	0.217
Vocal cord palsy (N, %)			
Permanent	0 (0)	1 (3.7)	> 0.999
Transient	5 (18.5)	3 (11.1)	0.704

Data are presented as the means ± SD, number (%). Abbreviations: *N*, number; *BMI*, Body Mass Index; *PTH*, parathyroid hormone.

thymectomy were allocated in the BT Group. The 2 groups were well-matched with respect to age, gender and BMI. (Table 1).

3.1. Clinical and histological characteristics

There were no significant differences in operative duration and hospitalization time between the two groups (p = 0.356 and p = 0.217, respectively). The incidence of transient vocal cord palsy failed to differ between the TP group and BT group (18.5% vs 11.1%, p = 0.704). Only 1 patient in the BT group with the violation of the recurrent laryngeal nerve eventually developed into permanent vocal cord palsy. All patients were eventually diagnosed as papillary thyroid cancer by pathological examination. No significant difference existed between the two groups with regards to tumor size, incidence of extracapsular invasion and multifocality (Table 1).

3.2. Function of parathyroid glands

PGs were present in the thyroid or central nodal specimens of 10 patients. Incidental parathyroidectomy was more common in patients undergoing thymectomy than in those who did not (29.6% vs 7.4%, p = 0.038). On postoperative day 1, the serum calcium and PTH levels dropped significantly in both groups. The BT group showed a greater decline (74.50% ± 15.95%) in mean serum PTH preoperatively to postoperative day 1 compared with the TP group (47.84% ± 25.19%) (p < 0.001). Neuromuscular symptoms occurred in 25 patients on postoperative day 1, a total of 8 patients in the TP group and 17 patients in the BT group. The incidence of neuromuscular symptoms was significantly higher in the BT group compared to the TP group (63.0% vs 29.6%, p = 0.014).

Postoperative transient hypoparathyroidism was observed in 26 patients; 7 (25.9%) in the TP group and 19 (70.4%) in the BT group. The incidence of transient hypoparathyroidism was significantly higher in the BT group compared to the TP group (p = 0.001). Twenty-two of these transient hypoparathyroidism patients with hypoparathyroidism achieved clinical resolution at the final follow-up visit. A total of four patients who both underwent bilateral thymectomy developed permanent hypoparathyroidism. The incidence of permanent hypoparathyroidism failed to show a significant difference between groups (p = 0.111). (Table 2).

Fig. 2 illustrates the changes of PTH of those with transient hypoparathyroidism in both groups. On postoperative day 1, serum PTH levels dropped significantly in both groups. Notably, the PTH level in the TP group was significantly higher than that in the BT group at 3 weeks postoperatively (p = 0.001), which demonstrated that PG function in the TP group recovered more rapidly to normal levels compared to the BT group (see Fig. 1).

Table 2
Perioperative parameters relating to the function of parathyroid glands in the TP group and BT group.

	TP group (n = 27)	BT group (n = 27)	P value
Incidental removed PGs (N, %)	2 (7.4)	8 (29.6)	0.038
In-hospital data			
Preoperative Serum PTH (pg/ml)	46.84 ± 9.33	44.84 ± 8.75	0.420
PO1 PTH (pg/ml)	25.46 ± 14.72	11.07 ± 6.03	< 0.001
Decreasing ratio of PTH (%)[1]	47.84 ± 25.19	74.50 ± 15.95	< 0.001
Neuronmuscular symptoms (N, %)	8 (29.6)	17 (63.0)	0.014
Hypoparathyroidism (N, %)			
Permanent	0 (0)	4 (14.8)	0.111
Transient	7 (25.9)	19 (70.4)	0.001

Data are presented as the means ± SD or number (%). Abbreviations: N, number; PGs, Parathyroid glands; PTH, parathyroid hormone; PO1 PTH, Serum iPTH on postoperative day 1.1 Decreasing ratio of PTH (%) = (preoperative PTH-postoperative PTH) × 100/preoperative PTH (%).

3.3. Surgical outcomes and oncological completeness

The median follow-up time was 9 months (range 6–11 months) for both groups. The follow-up response rate was 100%. No deaths occurred. There was no significant difference in the number of harvested lymph nodes between TP and BT groups (5.89 ± 3.12 vs 8.56 ± 6.93, p = 0.077). The ratio of central lymph nodes metastases was 51.9% in both groups.

^{131}I ablation was performed in 11 patients (20.4%), 7 in the TP group and 4 in the BT group. With regards to these patients undergoing ^{131}I treatment, there was no significant difference in preablation sTg between the TP and BT groups (1.82 ± 2.18 vs 1.42 ± 1.56, p = 0.775). Furthermore, there was no uptake in the extrathyroidal region in both groups, including the thymus. No residual thyroid glands or metastatic lymph nodes were found by sonography in both groups at 3 months postoperatively. (Table 3).

4. Discussion

In this study, total thyroidectomy with central lymph nodes dissection (CLND) was performed in patients with bilateral papillary thyroid cancer. PG function was impaired more commonly in the BT group compared with the TP group, with regards to the incidence of neuromuscular symptoms, transient hypoparathyroidism and PG incidental removal. Both groups witnessed a sharp decline in serum PTH followed by a slow increase postoperatively. However, the TP group had a higher serum PTH level within 3 weeks postoperatively and a shorter duration to clinical resolution of hypoparathyroidism compared with the BT group. No significant differences were found in oncologic completeness and recurrent laryngeal nerve injuries between groups.

Prophylactic CLND for cN0 patients is a controversial topic due to severe complications including hypocalcemia and recurrent laryngeal nerve injuries. In our department, we recommend that patients with bilateral papillary thyroid cancer should receive bilateral CLND considering the risk of lymph nodes metastases. A meta-analysis by Feng et al. [12] showed that two tumor foci was an independent factor for central lymph nodes metastases (CNM) in papillary thyroid cancer.

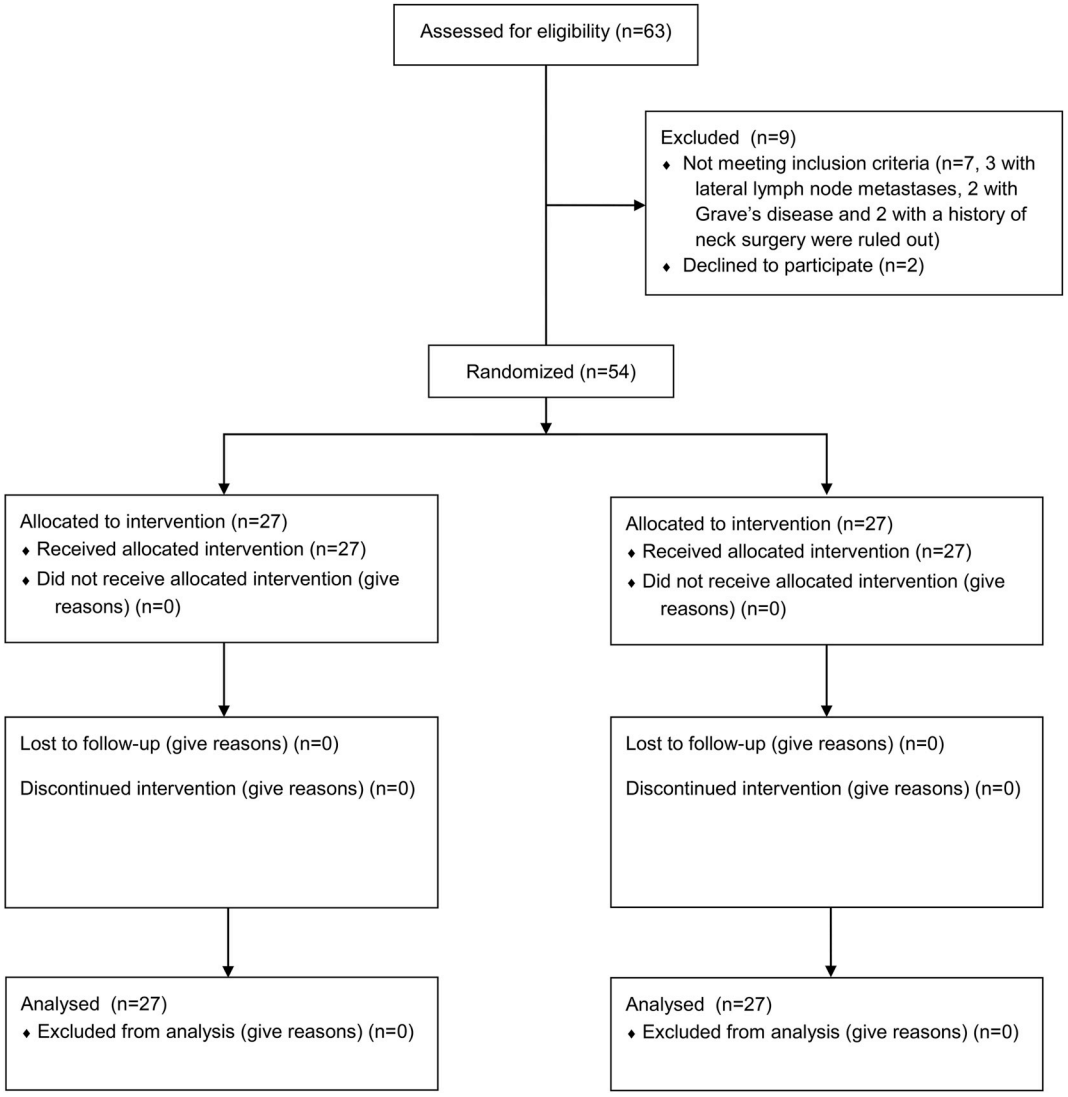

Fig. 1. Flow chart of the study.

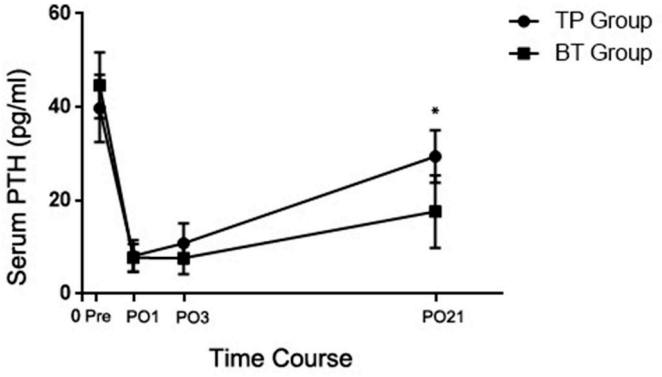

Fig. 2. Changes in PTH level of those with transient hypoparathyroidism postoperatively. Serum PTH in the BT group was significantly lower than that in TP group (17.63 ± 7.77 vs 29.43 ± 5.6 pg/ml, p = 0.001) at 3 weeks postoperatively. Abbreviations: *Pre*, preoperative PTH level; *PO1*, PTH level at the 1st day postoperatively; *PO3*, PTH level at the 3rd day postoperatively; *PO21*, PTH level at 3 weeks postoperatively. *P < 0.05.

Table 3
Comparisons of surgical completeness between the TP group and BT group.

	TP group (n = 27)	BT group (n = 27)	P value
Pathology data of LNs			
LNs resected (N)	5.89 ± 3.12	8.56 ± 6.93	0.077
Number of metastatic LNs (N)	1(0–7)	1(0–15)	0.775
LNs involvement (N, %)	14 (51.9)	14 (51.9)	> 0.999
Radioactive iodine treatment			
Yes (N, %)	7 (25.9)	4 (14.8)	0.311
No (N, %)	20 (74.1)	23 (85.2)	
Preablation sTg			
Mean (ng/ml)	1.82 ± 2.18	1.42 ± 1.56	0.775
< 1.0 ng/ml (N, %)	5 (71.4)	3 (75.0)	> 0.999
≥ 1.0 ng/ml (N, %)	2 (28.6)	1 (25.0)	
Uptake in the extrathyroidal region (N, %)	0 (0)	0 (0)	/
Metastatic LNs on sonography at 3 months (N, %)	0 (0)	0 (0)	/

Data are presented as the means ± SD, median (minimal-maximal), number (%). Abbreviations: *N*, number; *LNs*, lymph nodes; *sTg*, serum stimulated thyroglobulin.

Similar findings have been reported by other studies [13]. Studies have shown that the risk of recurrent laryngeal nerve injuries could be significantly reduced by exposure of recurrent nerve [14]. In our study, recurrent laryngeal nerve injury was found in 1 case with violation of the recurrent laryngeal nerve, which was unavoidable to achieve complete resection. However, protecting the function of PGs during CLND is still a challenge to surgeons.

Injuries to PGs, including incidental removal and devascularization, are the main causes leading to transient hypoparathyroidism after CLND [8,15]. Our data demonstrated that injuries to PGs were more common in BT group. This could be attributed to the embryologic and anatomic relationship between the thymus and PGs. Normally, the thymus originates from the pharyngeal pouch III and two pairs of PGs derive from the endoderm of pharyngeal pouches III and IV, respectively. Similarities in embryologic origin contribute to shared blood supply of thymus and PGs [7]. Thymus preservation could largely protect the blood supply of PGs, characterized by the decreased rate of hypoparathyroidism as well as the faster recovery of postoperative serum iPTH in our study [16]. Furthermore, during the development of PGs, either delayed separation or aberrant migration could lead to ectopic inferior PGs, most of which were frequently found in the thymus [17,18]. In our study, the rate of incidental parathyroidectomy was higher in BT group ($p = 0.038$), implying that thymus preservation might reduce the removal of PGs which possibly located in thymus.

There was no significant difference with respect to the prevalence of permanent hypoparathyroidism between groups. The incidence of permanent hypoparathyroidism was reported to be from 2.3% to 30% in previous studies [19–21]. In the present study, the incidence of permanent hypoparathyroidism was low because of the small incidental parathyroidectomy ratio (7.41% in TP group and 29.6% in BT group) and careful preservation of the superior PGs. It can be inferred that PGs left *in situ* are the most influential in long-term function of PGs. This is in agreement with Lorente-Poch et al., who stated that long-term postoperative PG function mainly depends on the number of PGs remaining *in situ* after thyroidectomy [22]. Stimulated by hypocalcemia, the remaining PGs are able to maintain PTH values within the normal range [23].

Studies have shown that the number of harvested lymph nodes and serum sTg are the two most reliable indices for the evaluation of oncological completeness [24]. In this study, there was no significant difference in the number of retrieved lymph nodes between TP and BT groups (5.89 ± 3.12 vs 8.56 ± 6.93, $p = 0.077$). Moreover, no significant differences were found in the level of preablation serum sTg and the proportion of patients with serum sTg < 1 ng/ml. The mean levels of preablation serum sTg in TP group and BT group were 1.82 ± 2.18 ng/ml and 1.42 ± 1.56 ng/ml, which was in agreement with the results reported by Lee et al. [25] and Chai et al. [26]. Given the fact that sTg was only checked in a total of 11 (20.37%) patients who received RAI, ultrasound scans were performed on all patients at 3 months postoperatively. No residual thyroid glands or metastatic lymph nodes were found in both groups.

Although there exists a blood-thymus barrier, metastasis to the thymus is possible from the breast [27], colon [28], and thyroid [9]. In the present study, no thymic metastases were found in our study. Though approximately 3.4%–26.3% patients have been reported to have thymus visualization on ^{131}I scintigraphy after surgery, no metastases were found among these patients [29]. In addition, partly owing to thymic hyperplasia, false positive images increase the difficulty of detecting mediastinal metastasis as well as radiotherapy [30]. Pathologic metastasis to the thymus in thyroid cancer were only reported in patients with an ectopic thymus or high incidence of lymphatic spread [9,31]. Given these findings, surgeons should make decisions according to the anatomic and pathologic characteristics of the thymus intraoperatively.

There are, however, some study limitations. First, this was a single institution study, which limited the sample size; thus, the population who underwent RAI was small. Comparison of sTg in these patients might not be reliable. Consequently, multiple indices were regarded in the evaluation of oncological completeness. On the other hand, it was unknown whether thymic metastases would be examined if sample size in the group was larger. Second, the follow-up period was too short to obtain convincing data on recurrence and metastasis of PTC. Prospective and randomized trials with larger sample sizes and relatively long-term follow-up periods are necessary to assess the exact clinical role of thymus preservation during bilateral CLND for PTC.

5. Conclusions

In conclusion, thymus preservation was closely associated with protecting PGs and promoting rapid clinical resolution of hypoparathyroidism. It had no effects on oncologic completeness of TT with bilateral CLND. Since thymic metastases failed to be examined, our findings suggest that thymus preservation should be performed during TT with bilateral CLND unless multiple lymph node metastasis surrounding thymus or multiorgan metastases. Future studies should focus on recurrence rates and patterns of both groups.

Ethical approval

The study protocol was approved by our institutional Ethics Committee and written informed consent was obtained from each participant. The approved number of ethic committee is CZEC (2016)-20.

Author contribution

Wei Li: Formal Analysis, Writing – Original Draft.
Bin Wang: Software, Writing – Review & Editing, Funding Acquisition.
Zhiguo Jiang: Investigation.
Yunjie Feng: Data Curation, Resources.
Wei Zhang: Methodology, Project Administration.
Ming Qiu: Conceptualization, Supervision, Project Administration.
Contributors: Xing-zhu Wen for assistance in data collection, Xiao-xia Cen for assistance in statistical analysis and Xiao-fei Ye for generating the random allocation sequence.

Conflicts of interest

None.

Research registration unique identifying number (UIN)

This study was registered on the ChiCTR (Chinese Clinical Trial Registry, http://www.chictr.org.cn/) database (No. ChiCTR-INR-16010037).

Guarantor

Wei Zhang and Ming Qiu.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data statement

Data of this article will be made available on request.

CRediT authorship contribution statement

Wei Li: Formal analysis, Writing - original draft, Validation, Visualization. **Bin Wang:** Formal analysis, Writing - original draft, Validation, Visualization. **Zhi-guo Jiang:** Investigation, Formal analysis. **Yun-jie Feng:** Data curation, Resources. **Wei Zhang:** Methodology, Project administration, Supervision. **Ming Qiu:** Conceptualization, Supervision, Project administration.

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Appendix A. Supplementary data

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