

# Protective strategy of parathyroid glands during thyroid lobectomy

## A retrospective cohort and case-control study

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### Abstract

Parathyroid protection during thyroid lobectomy was not illustrated previously. Aim of this study was to find out the influence of parathyroid glands in situ preservation and autotransplantation on postoperative parathyroid function in thyroid lobectomy.

Consecutive patients who underwent primary thyroid lobectomy with unilateral central neck dissection for papillary thyroid carcinoma in our center were included retrospectively. Postoperative hypoparathyroidism was defined as low parathyroid hormone (PTH) levels ( $<1.6$  pmol/L) and keeping over 6 months was defined as permanent. Patients were divided into 3 groups: all identified parathyroid glands preserved in situ (preservation group); at least one parathyroid gland autotransplanted without accidental resection (autotransplantation group); at least one parathyroid gland accidental resected (resection group).

A total of 425 patients were included. No permanent hypoparathyroidism was reported, and the rates of transient hypoparathyroidism were similar among all groups. Significantly lower serum PTH levels were found in autotransplantation group versus preservation group at postoperative 1-day ( $3.77 \pm 1.61$  vs  $4.72 \pm 2.31$ ,  $P < .001$ ). Transient hypoparathyroidism was significantly associated with reduced intraoperative carbon nanoparticles utilization (57.1% vs 77.4%,  $P = .039$ ).

Thyroid lobectomy was a safe surgical method for parathyroid protection no matter the practice to ipsilateral parathyroid glands. However, preservation of all parathyroid glands was still recommended considering relatively stable PTH levels.

**Abbreviations:** AJCC = American Joint Committee on Cancer, BMI = body mass index, CI = confidence interval, GD = Grave disease, HD = Hashimoto disease, NG = nodular goiter, OR = odds ratio, PTC = papillary thyroid carcinoma, PTH = parathyroid hormone, ROC = receiver operator characteristic, TT = total thyroidectomy.

**Keywords:** autotransplantation, hypoparathyroidism, parathyroid glands, thyroid lobectomy

## 1. Introduction

The incidence of thyroid cancer has increased 3-fold from 4.9 per 100,000 to 14.3 per 100,000 over the past 3 decades, and almost the entire change has been attributed to an increase in the incidence of papillary thyroid carcinoma (PTC).<sup>[1,2]</sup> Total

thyroidectomy (TT) with central neck dissection has been widely adopted for the treatment of PTC in many cases, while it increases the risk of postoperative hypoparathyroidism, especially for patients with bilateral central neck dissection.<sup>[3]</sup> Nevertheless, studies suggested that thyroid lobectomy alone may be a sufficient initial treatment for low risk PTC which maximum size  $<1$  cm and without extrathyroidal extension or lymph node metastasis.<sup>[4]</sup> Several studies demonstrated non-inferior overall survival for differentiated thyroid cancer patients with low-risk cancer who underwent thyroid lobectomy compared with those patients who had TT.<sup>[5]</sup> Therefore, thyroid lobectomy is used more widely and it is reported it increased significantly after the release of the 2015 American Thyroid Association guidelines.<sup>[4,6]</sup> What's more, the surgical risk of thyroid lobectomy is lower than TT, with a meta-analysis suggesting a pooled relative risk significantly lower for all complications, such as recurrent laryngeal nerve injury, hypocalcemia, and hemorrhage.<sup>[7]</sup>

Despite this, unilateral parathyroid injury from devascularization, mechanical and thermal trauma, or resection of  $\geq 1$  parathyroid glands is unavoidable during thyroid lobectomy,<sup>[8-11]</sup> resulting in decreases in serum calcium and parathyroid hormone (PTH). Therefore, strategy of parathyroid glands protection is still an important issue during thyroid lobectomy. However, previous studies about the protective strategy of parathyroid glands was almost based on TT,<sup>[12-14]</sup> and no special illustration about thyroid lobectomy was stated. Therefore, the aim of this study was to discuss the influence of in situ

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preservation, autotransplantation, and accidental parathyroidectomy on parathyroid glands function in thyroid lobectomy.

## 2. Methods

### 2.1. Patients

We reviewed our clinical database containing 2032 consecutive records of patients with PTC in the Department of Thyroid & Parathyroid Surgery, West China Hospital, Sichuan University between January 2013 and June 2018, retrospectively. PTC was finally confirmed by postoperative pathology. All the patients who underwent primary thyroid lobectomy with unilateral central neck dissection were included. The Institutional Review Board of West China Hospital approved this retrospective study, and all patients provided informed consent to have their data recorded, analyzed, and published for research purposes.

Patients were divided into 3 groups: in situ preservation of all identified parathyroid glands (preservation group); autotransplantation with no accidental parathyroidectomy (autotransplantation group); accidental parathyroidectomy (resection group).

Exclusion criteria included incomplete data. Reoperation. Kidney disease. Endoscopic thyroidectomy. Patients with preoperative hyperparathyroidism or hypoparathyroidism.

### 2.2. Indications and surgical procedures

All surgeries were performed by an experienced surgeon team and carbon nanoparticles suspension was injected into the thyroid gland to facilitate parathyroid glands identification according to each patient's will.<sup>[15]</sup> The indications for thyroid lobectomy are as follows<sup>[4]</sup>: low risk cancer (no clinical or radiographic evidence of invasion or metastases) or papillary microcarcinomas (<1 cm) without clinically evident metastases or local invasion, and no convincing cytologic or molecular evidence (if performed) of aggressive disease. Unilateral central neck dissection is performed routinely. During operation, attempt was firstly made to preserve all parathyroid glands and autotransplantation will be performed when the parathyroid gland was discolored at the end of the surgery or was incidentally removed during the operation, which will be chopped into 1 mm<sup>[3]</sup> fragments and then autografted into several pockets in the ipsilateral sternocleidomastoid muscle. All the specimens removed would be systematically dissected in case intra-thyroid parathyroid glands being unintentionally resected. Identification of parathyroid glands was based on visual features. The parathyroid gland would be verified by intraoperative frozen-section biopsy when in doubt. The number of parathyroid glands identified and autotransplanted, in situ preserved was recorded in operative notes. All surgical specimens were analyzed by the same pathologist and the presence of parathyroid glands accidentally resected in the surgical specimens was recorded.

### 2.3. Perioperative evaluation and follow-up

Demographic data were collected upon admission. Serum parathyroid hormone (PTH, pmol/L) were measured at 1-day, 1-month, 6-month follow-up. Patients were given prophylactically intravenous 4000 mg calcium gluconate supplementation after operation. Then patients with normal calcium complained no discomfort were discharged on the 1st or 2nd postoperative day. Patients were followed up in the outpatient department.

### 2.4. Definition

Postoperative hypoparathyroidism was defined as a PTH level <1.6 pmol/L (normal range, 1.6–6.9 pmol/L), regardless of hypocalcemia symptoms. If PTH level returned to normal within 6 months after surgery, hypoparathyroidism was defined as transient. Permanent hypoparathyroidism was defined if it lasted >6 months. The number of identified parathyroid glands was defined based on visual features or intraoperative frozen-section biopsy and the parathyroid glands would be preserved in situ or autotransplanted after that. We defined accidental parathyroidectomy as the presence of a whole parathyroid gland or parathyroid tissue fragments ( $\geq 1$  mm) in the specimen confirmed by pathological section examination postoperatively.

### 2.5. Data collection

All data were collected retrospectively, including demographic data and basic information: age, sex, body mass index (BMI), nodular goiter (NG), Hashimoto disease (HD), Grave disease (GD), hypertension, diabetes, hyperthyroidism, hypothyroidism; oncological data: tumor size, multifocality, TNM stage, capsule invasion; preoperative examination; the number of parathyroid glands identified, autotransplanted, resected in the surgical specimens was recorded in all cases. The levels of PTH at long-term follow-up, the rates of hypoparathyroidism were primary endpoints. American Joint Committee on Cancer (AJCC) staging (the 8th edition) was applied for all PTC patients.<sup>[16,17]</sup>

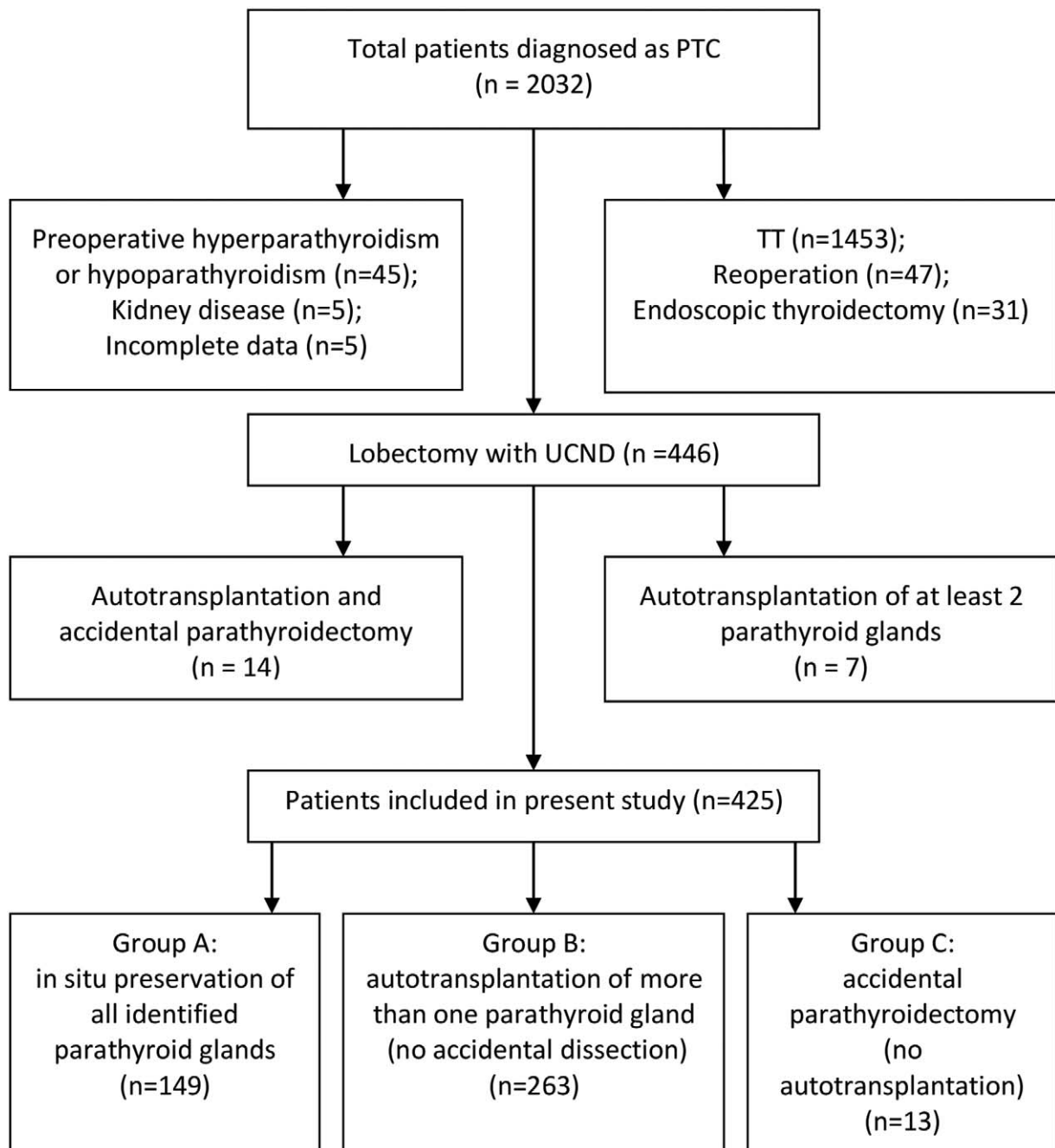
### 2.6. Statistical analysis

If normally distributed, continuous variables were expressed as mean  $\pm$  standard deviation and evaluated by the student *t* test and/or analysis of variance; if not normally distributed, variables were presented as median (interquartile range) and compared by *U* test. The Chi-squared test or Fisher exact test was used to evaluate the differences of incidences. Based on the variables that were statistically significant or *P* value <.10 in univariate analysis, multivariate analysis with logistic regression was conducted to identify the independent risk factors. The results of the multivariate analysis were reported in odds ratio (OR) and 95% confidence interval (CI). Two-sided *P* <.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 25.0 for Windows (IBM Corp., Armonk, NY).

## 3. Results

### 3.1. Patient characteristics

Of the 2032 patients whose medical records were reviewed, 425 patients were included with an age of  $41.2 \pm 11.23$  years (Fig. 1). All patients underwent thyroid lobectomy with unilateral central neck dissection. There were 304 (69.9%) women and 131 (30.1%) men. Preservation group, autotransplantation group, and resection group consisted of 149, 263, and 13 patients, respectively. Baseline characteristics were shown in Table 1. No significant difference was found between preservation group and autotransplantation group, autotransplantation group and resection group about age, sex, BMI, NG, HD, GD, hypertension, diabetes, hypothyroidism, hyperthyroidism. As for the characteristic of tumors, no significant difference was found between preservation group and autotransplantation group, autotrans-



**Figure 1.** Flow chart of patients reviewed. PTC=papillary thyroid carcinoma, TT=total thyroidectomy, UCND=unilateral central neck dissection.

plantation group and resection group about largest tumor size, multifocality, capsule invasion, T classification, preoperative levels of serum PTH, and calcium. Intraoperative use of carbon nanoparticles were significantly higher in preservation group than autotransplantation group (82.5% vs 49.0%,  $P < .001$ ).

### 3.2. Details of parathyroid glands, hypoparathyroidism and follow-up

Significantly more parathyroid glands were identified in patients with autotransplantation group versus resection group ( $1.91 \pm 0.22$  vs  $1.08 \pm 0.49$ ,  $P < .001$ ). No patients suffered from

permanent hypoparathyroidism in the entire cohort, and the rates of transient hypoparathyroidism was 4.41% (6/136) in preservation group, 7.27% (12/165) in autotransplantation group, and 7.69% (1/13) in resection group, respectively ( $P > .05$ ). The serum PTH levels in the 3 groups during 6-month follow-up were showed in Table 2. Significantly lower serum PTH levels (pmol/L) were found in autotransplantation group versus preservation group at postoperative 1-day ( $3.77 \pm 1.61$  vs  $4.72 \pm 2.31$ ,  $P < .001$ ). No significant difference was found among the PTH levels of 3 groups at postoperative 1-month and 6-month ( $P > .05$ ). The recovery rates of serum PTH levels were 86.27%, 82.06%, and 73.51% in the 3 groups.

**Table 1**  
Demographics and baseline characteristics of patients.

	Preservation group (n = 149)	Autotransplantation group (n = 263)	Resection group (n = 13)	P value*	P value†
Age, y	42.34 ± 11.34	40.37 ± 10.82	44.92 ± 15.22	.082	.307
Sex, male/female	54/95	71/192	4/9	.050	1.000
BMI, kg/m <sup>2</sup>	22.83 ± 3.07	22.81 ± 3.52	22.97 ± 4.57	.940	.874
NG	27/149	44/263	4/13	.719	.353
HD	17/149	47/263	3/13	.082	.915
GD	0/149	1/263	0/13	1.000	1.000
Hypertension	12/149	26/263	3/13	.537	.293
Diabetes	3/149	6/263	1/13	1.000	.758
Hypothyroidism	2/149	6/263	1/13	.770	.758
Hyperthyroidism	3/149	2/263	0/13	.517	1.000
Largest tumor size, mm	8.53 ± 5.14	8.71 ± 4.93	11.35 ± 8.96	.744	.112
Multifocality	20/149	38/263	1/13	.774	.783
Capsule invasion	9/149	23/263	2/13	.324	.750
Carbon nanoparticles	85/103 (82.5%)	98/200 (49.0%)	5/11 (45.5%)	<.001‡	.819
TNM stage					
T1a/T1b/T2	118/12/11	210/33/13	10/1/2	.261	.373
Preoperative PTH, pmol/L	6.12 ± 2.34	6.19 ± 3.69	8.53 ± 6.21	.848	.201
Preoperative calcium, mmol/L	2.36 ± 0.32	2.33 ± 0.14	2.41 ± 0.15	.135	.061

BMI = body mass index, GD = Grave disease, HD = Hashimoto disease, NG = nodular goiter, PTH = parathyroid hormone.

\* Preservation group versus autotransplantation group.

† Autotransplantation group versus resection group.

‡ Means significantly statistical differences.

### 3.3. Risk factors for transient hypoparathyroidism

As shown in Table 3, transient hypoparathyroidism was significantly associated with lower rates of carbon nanoparticles utilization intraoperatively (57.1% vs 77.4%,  $P = .039$ ). However, no independent risk factor for transient hypoparathyroidism was found in multivariate analysis (Table 4).

## 4. Discussion

In this study, we evaluated the rates of postoperative hypoparathyroidism and PTH levels according to the strategy of parathyroid gland protection in thyroid lobectomy. To the best of our knowledge, no study investigated parathyroid autotransplantation or preservation in thyroid lobectomy.

It seems to have reached a consensus that autotransplantation increased the risks of transient hypoparathyroidism,<sup>[13]</sup> and it is still controversial whether it can reduce the incidence of permanent hypoparathyroidism.<sup>[18–20]</sup> Some authors demonstrated no relationship between the incidence of permanent

hypoparathyroidism and the number of parathyroid glands autotransplanted,<sup>[18]</sup> while other authors believed that autotransplantation may be the best strategy to prevent permanent hypoparathyroidism.<sup>[18–20]</sup> However, these results were all based on total thyroidectomy. The strategy of parathyroid glands protection in hemithyroidectomy might be different although it could be referred to the results of total thyroidectomy. In present study, no patients suffered from permanent hypoparathyroidism after thyroid lobectomy. This finding was consistent with previous studies reported that preserving at least 2 parathyroid glands with an intact blood supply was sufficient to prevent permanent hypoparathyroidism.<sup>[21]</sup> In our study, the rate of transient hypoparathyroidism has a higher trend in patients with autotransplantation and accidental parathyroidectomy than patients with all parathyroid glands preserved in situ, but the difference did not reach statistical significance. Lower serum PTH levels were found in patients with autotransplantation of at least 1 parathyroid gland than patients with all parathyroid glands preserved in situ at postoperative 1-day. However, the PTH levels became similar among the 3 groups at postoperative 1-month and

**Table 2**  
The details of parathyroid glands function during follow-up.

	Preservation group	Autotransplantation group	Resection group	P value*	P value†
No. of identified PGs	1.84 ± 0.37	1.91 ± 0.22	1.08 ± 0.49	.339	<.001‡
Hypoparathyroidism					
Transient	6/136 (4.41%)	12/165 (7.27%)	1/13 (7.69%)	.298	1.000
Permanent	0	0	0	–	–
Postoperative PTH, pmol/L					
1 day	4.72 ± 2.31	3.77 ± 1.61	4.60 ± 4.66	<.001‡	.568
1 month	5.41 ± 2.85	5.13 ± 1.80	6.51 ± 4.78	.341	.338
6 months	5.28 ± 1.78	5.08 ± 1.72	6.27 ± 4.51	.570	.357

No. of identified PGs = number of identified parathyroid glands, PTH = parathyroid hormone.

\* Preservation group versus autotransplantation group.

† Autotransplantation group versus resection group.

‡ Means significantly statistical differences.

**Table 3****Univariate analysis of risk factors for transient hypoparathyroidism.**

	Normal	Transient hypoparathyroidism	P
Age, y	41.61 ± 11.43	39.19 ± 12.64	.353
Sex, male/female	97/204	3/18	.086
BMI, kg/m <sup>2</sup>	23.02 ± 3.59	21.51 ± 3.47	.064
NG	56/301	2/21	.451
HD	57/301	2/21	.432
GD	0/301	1/21	1.000
Hypertension	31/301	2/21	1.000
Diabetes	8/301	1/21	1.000
Hypothyroidism	9/301	0/21	.905
Hyperthyroidism	4/301	1/21	.751
Largest tumor size, mm	9.00 ± 5.83	8.50 ± 3.34	.710
Multifocality	44/301	4/21	.815
Capsule invasion	22/301	0/21	.403
Carbon nanoparticles	168/217 (77.4%)	12/21 (57.1%)	.039*
TNM stage			
T1a/T1b/T2	238/30/22	18/0/1	.118
Preoperative PTH, pmol/L	6.32 ± 3.82	6.35 ± 2.57	.952
Preoperative calcium, mmol/L	2.36 ± 0.23	2.34 ± 0.16	.752
No. of identified PGs	1.86 ± 0.36	1.84 ± 0.38	.856
No. of autotransplanted PGs ≥ 1	159/301	13/21	.420
Accidental parathyroidectomy	12/301	1/21	1.000

BMI=body mass index, GD=Grave disease, HD=Hashimoto disease, NG=nodular goiter, PGs=parathyroid glands, PTH=parathyroid hormone.

\*Means significantly statistical differences.

6-month. By the end of the follow-up, the parathyroid function recovered to preoperative levels in most of the patients in the 3 groups. A study reported that accidental resection of >2 parathyroid glands was a risk factor for transient hypoparathyroidism.<sup>[11]</sup> However, only 13 of 425 cases reported accidental dissection of 1 parathyroid glands and only 1 reported transient hypoparathyroidism in present study. These results revealed the safety of thyroid lobectomy for the protection of parathyroid function. During thyroid lobectomy, the incidence of transient and permanent hypoparathyroidism would not increase whether the parathyroid glands of the operative side were preserved in situ, or one was autotransplanted, or resected accidentally when the contralateral parathyroid glands were not injured. A study reported complications occurrence varied according to the surgical extent.<sup>[22]</sup> Patients who underwent TT had significantly more transient (15% vs 0%) and permanent (1.7% vs 0%) hypoparathyroidism than lobectomy. In addition, there were no significant differences in recurrence-free survival between the 2 groups after the exclusion of contralateral lobe recurrences. Another study reported that unilateral lobectomy was a safe operative option for selected patients with unilateral, multifocal, node-negative papillary microcarcinomas according to locoregional recurrence and incidence of transient hypocalcemia.<sup>[23]</sup>

**Table 4****Multivariate analysis of predictors for transient hypoparathyroidism.**

	OR	95% CI	P value
Female	2.192	0.853–5.632	.103
BMI < 22 kg/m <sup>2</sup>	2.439	0.682–8.724	.170
No carbon nanoparticles	2.672	0.987–7.228	.053

CI=confidence interval, OR=odds ratio.

Intraoperative utilization of carbon nanoparticles was more in patients with all parathyroid glands preserved in situ than patients with autotransplantation of one parathyroid gland. We believed that carbon nanocarbons could help identify parathyroid glands and avoid accidental parathyroidectomy, which was consistent with previous studies.<sup>[24–29]</sup> Therefore, the higher utilization rate of carbon nanoparticles in patients with all parathyroid glands preserved in situ could be explained. Additionally, transient hypoparathyroidism was significantly associated with less use of carbon nanoparticles in univariate analysis. In addition to carbon nanoparticles, others methods could also protect the parathyroid glands, such as anatomical localization of normal parathyroid glands before thyroidectomy through ultrasonography, using of loupes magnification and microsurgical technique in thyroid surgery, Technetium (Tc99m)-sestaMIBI as radiotracer for intraoperative localization of parathyroid glands.<sup>[30–32]</sup> Previous studies reported female sex, older age, bilateral central neck dissection, autotransplantation of parathyroid glands, and incidental parathyroidectomy might be risk factors for transient hypoparathyroidism in TT.<sup>[13,33–35]</sup> However, no factor associated with transient hypoparathyroidism was found in present study in multivariate analysis based on thyroid lobectomy. This also confirmed that thyroid lobectomy was safe for parathyroid glands protection.

There are some limitations in the present study. There was possibility of selection bias due to its retrospective nature and the involvement of only our single tertiary referral center. The sample size was not large enough and the number of accidental parathyroidectomy cases was small.

In conclusion, thyroid lobectomy was a safe surgical method for parathyroid protection no matter the practice to ipsilateral parathyroid glands. However, preservation of all parathyroid glands was still recommended considering relatively stable PTH levels.

**Author contributions**

Zhichao Xing, Yuxuan Qiu: study design, data collections, data analysis and drafting the article, final approval of the version to be submitted.

Yuan Fei, Baoying Xia, Munire Abuduwaili: acquisition of data, data analysis.

Jingqiang Zhu and Anping Su: study design, revising the manuscript, final approval of the version to be submitted.

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