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HEAD AND NECK

Efficacy of hemithyroidectomy in papillary thyroid carcinoma with minimal extrathyroidal extension

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Abstract

Purpose This study aimed to compare the oncologic outcomes of hemithyroidectomy with total thyroidectomy in clinically node-negative (cN0) papillary thyroid carcinoma (PTC) with minimal extrathyroidal extension (ETE).

Methods Among 1826 PTC patients who underwent thyroidectomy from Jan 2001 to Dec 2014, there were 255 with unilateral cN0 PTC with minimal ETE and of equal to or less than 2 cm in size; these 255 patients were included in this study. We excluded patients who had tumor size > 2 cm, bilateral tumors, clinically positive nodes, maximal or no ETE, gross invasion of sternothyroid muscle, recurrent cancers or distant metastases. Total thyroidectomy was performed in 173 of the 255 patients, and hemithyroidectomy in 82 of them. A propensity score-matched analysis was carried out to reduce selection bias, with the following covariates: sex, age, tumor size, multiplicity and central neck dissection.

Results In the baseline data of the 255 patients, female, age and tumor size were significantly higher in the total thyroidectomy group as was Stage III, whereas T and N classification did not differ in the two groups. Propensity score matching generated two matched groups of 66 patients each, in which the significant differences between the two groups seen in the baseline analysis disappeared. In the matched samples, recurrence rate (3.0% vs. 1.5%, $p = 1.0$) and recurrence-free survival curves did not differ between total thyroidectomy and hemithyroidectomy.

Conclusions Hemithyroidectomy can be recommended for cN0 PTC 1 cm or less with minimal ETE. Also it can be considered for cN0 PTC 11–20 mm with minimal ETE.

Keywords Papillary thyroid carcinoma · Hemithyroidectomy · Extrathyroidal extension · Recurrence · Propensity score matching

Introduction

Extrathyroidal extension (ETE) outside the thyroid capsule is an important prognostic factor for papillary thyroid carcinoma (PTC). It is associated with a higher risk of recurrence and persistent disease, an increased likelihood of lymph node metastasis, and lower survival [1–4]. Hence ETE is included in various staging systems for prognosis of thyroid cancer, such as MACIS (metastasis, age, completeness of resection, invasion, and size), EORTC (European Organization for Research and Treatment of Cancer), AMES (age, metastasis, ETE, and size), AGES (age, grade, ETE, and size), and the AJCC (American Joint Committee on Cancer) TNM staging system [5–9]. However, ETE ranges from gross invasion of major structures (trachea, larynx, recurrent laryngeal nerve, and esophagus, etc.) to minor extension through the thyroid capsule.

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PTC with gross ETE has worse oncologic outcomes than PTC with microscopic ETE [10–13]. Actually minimal ETE is not an independent prognostic factor for recurrent/persistent disease [14–21]. Minimal ETE (e.g., extension to the perithyroidal soft tissue or sternothyroid muscle) is distinguished from maximal ETE since the 6th edition of the AJCC cancer staging system [22].

Hemithyroidectomy (lobectomy) is safe in low-risk PTC patients [23–26]. and its indications in clinical guidelines have been widened in the last decade [27–30]. The American Thyroid Association (ATA) and British Thyroid Association (BTA) guidelines recommend it for clinically node-negative (cN0) thyroid cancer < 1 cm without ETE. Both lobectomy and total thyroidectomy are allowed for cN0 patients with tumor size > 1 cm and < 4 cm without ETE [27, 28]. The Japanese Society of Thyroid Surgeons (JSTS) recommends total thyroidectomy for PTC > 4 cm, and lobectomy for cN0 PTC ≤ 2 cm [29]. The NCCN guideline also regard cN0 PTC of 4 cm or less without ETE as a candidate for lobectomy [30].

However, generally thyroid lobectomy is not recommended for PTC with ETE regardless of the extent of the ETE in current clinical guidelines. The optimal extent of thyroidectomy for PTC with microscopic or minimal ETE is debatable, and the definition of ETE is also not clear in most guidelines.

If minimal ETE were not an independent poor prognostic factor and did not affect recurrence and/or survival, hemithyroidectomy might be justified for unilateral PTC with minimal ETE to reduce surgical morbidity related with total thyroidectomy. However, there is no study to evaluate the effectiveness of hemithyroidectomy in PTC larger than 1 cm with minimal ETE comparing with total thyroidectomy. Therefore, we initiated the present study to compare the oncologic outcomes of hemithyroidectomy with total thyroidectomy for clinically node-negative PTC < 4 cm with minimal ETE.

Materials and methods

Patients

This retrospective study was conducted in a tertiary care university hospital. This study was approved by the institutional review board and informed consent was waived. We reviewed 1826 consecutive PTC patients who underwent thyroidectomy from Jan 2001 to Dec 2014. To include only unilateral cN0 PTC patients of less than 4 cm with minimal ETE, we excluded 1484 of the 1826 PTC patients who had tumors ≥ 4 cm, preoperative clinical lymph node metastasis, bilateral carcinoma, no ETE, maximal ETE, distant metastasis, or who underwent revision/completion thyroidectomy or concurrent lateral selective neck dissection.

Minimal ETE was defined as the primary tumor extending through the thyroid capsule and confined to perithyroidal soft tissue or the strap muscle. Maximal ETE was defined as the tumor extending to surrounding structures such as larynx, trachea, esophagus, recurrent laryngeal nerve, subcutaneous soft tissue, skin, internal jugular vein, or carotid artery [22]. All surgical specimens were reviewed by two experienced pathologists. Clinically node-negative neck was defined as no suspicious lymph node on imaging study of ultrasonography (US) and neck computed tomography (CT) scan with contrast enhancement regardless of cytological confirmation.

From the remaining 342 PTC patients with minimal ETE, we also excluded those with tumors > 2 cm or tumors with gross invasion of the sternothyroid muscle because only one patient with tumor > 2 cm underwent hemithyroidectomy, and all the patients with gross invasion of the sternothyroid muscle had received total thyroidectomies. Finally, we included 255 PTC patients with unilateral cN0 tumors ≤ 2 cm and minimal ETE. Of these patients, 173 underwent total thyroidectomy and 82 underwent hemithyroidectomy. In our institute, the extent of thyroidectomy for PTC with minimal ETE was determined according to various factors including tumor size, the presence of tumors in the contralateral lobe, surgeon's preference, patient's preference and the intraoperative presence and degree of ETE. Postoperative radioactive iodine (RAI) ablation was performed in all patients with maximal ETE regardless of tumor size, tumor size larger than 4 cm, or distant metastases, and also in some selected patients with minimal ETE or cervical lymph node metastasis, and higher risk histologic features among those who underwent total thyroidectomy. Figure 1 is a flow diagram of the patient selection process.

Physical examination, neck US, and serum thyroglobulin (TSH-stimulated or non-stimulated) measurements were performed to detect recurrence after surgery at 6–12 month intervals in all patients. Whole-body iodine scan was performed selectively in some patients who underwent total thyroidectomy and RAI ablation.

Recurrence was defined as the development of new abnormal structural lesions on imaging study, such as neck US, CT, or whole-body iodine scan, and loco-regional recurrence was confirmed pathologically using fine-needle aspiration cytology (FNAC).

Propensity score matching

We performed propensity score matching (PSM) to reduce the probability of selection bias and to adjust for significant differences in baseline characteristics between the total thyroidectomy and hemithyroidectomy groups. Propensity score

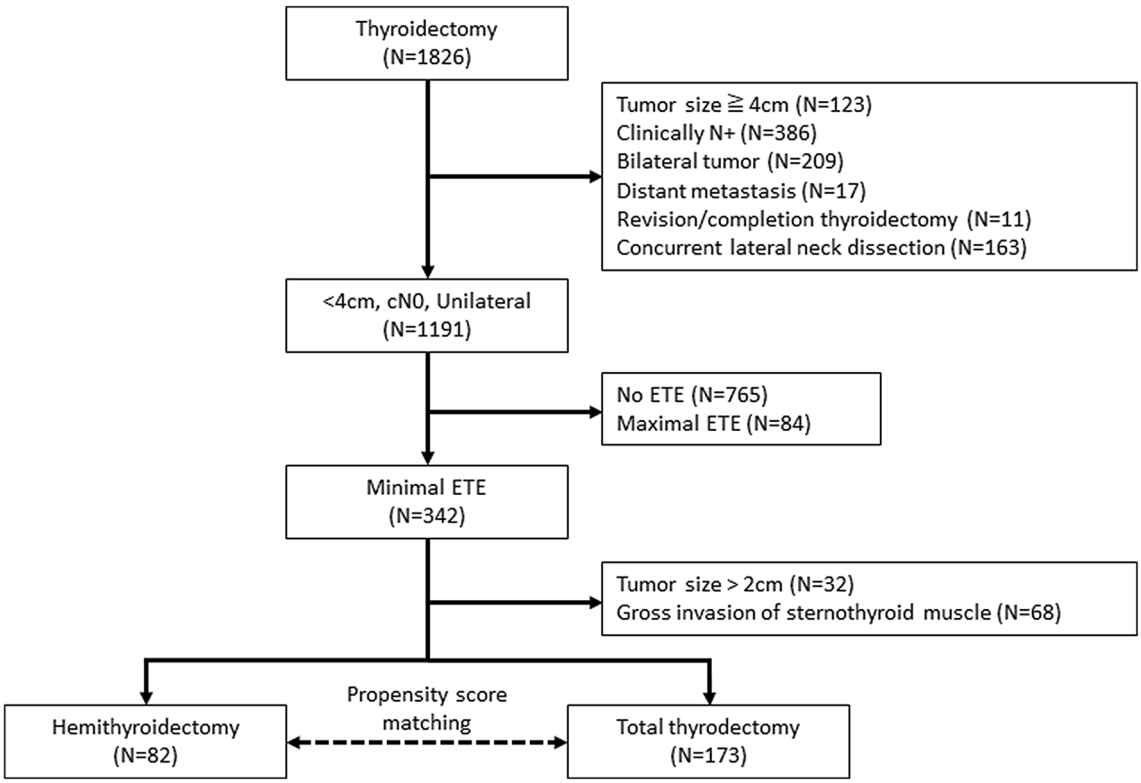

Fig. 1 Flowchart of patient selection

matching is a statistical matching technique that attempts to assess the effect of a treatment by accounting for the covariates that predict receiving the treatment [31, 32]. The patients' propensity scores were estimated using a logistic regression model based on the following five variables: sex, age, tumor size, multiplicity and central neck dissection (CND). Pairwise matching was performed without replacement, using nearest neighbor matching. Individuals were matched when their propensity score difference was less than 0.05. We excluded patients who did not have close pairs from the final matched subset. Sixty-six pairs of patients were generated after PSM and compared.

Statistical analysis

Continuous variables are expressed as means ± standard deviations (SD) and categorical variables as numbers (%). Continuous variables were compared with Student's *t* test, and categorical variables with Pearson's Chi square test or Fisher's exact test. Recurrence rates and recurrence-free survivals (RFS) were compared in the total thyroidectomy and hemithyroidectomy groups. Complication rate was also compared between the two groups as secondary surgical outcomes. We also divided the PSM groups into two subgroups according to tumor size (≤ 10 mm and 11–20 mm) and the presence of occult metastatic LN, and compared recurrence rates and RFS in the subgroups. The Kaplan–Meier method was used to evaluate RFS, and survival curves were compared by the log-rank test. All statistical analyses were performed with SPSS version 18.0 (SPSS Inc., Chicago, Illinois, USA) and $p < 0.05$ was considered statistically significant.

Results

Clinicopathologic characteristics of the baseline cohort

The baseline clinicopathologic characteristics of the 255 patients with cN0 PTC ≤ 2 cm and minimal ETE are summarized in Table 1. The gender distributions of the two groups were different. Mean age and tumor size were significantly higher in the total thyroidectomy group whereas multiplicity and lymphovascular invasion did not differ. CND was performed in 145/173 (83.8%) of the total thyroidectomy patients and 74/82 (90.2%) of the hemithyroidectomy patients. TNM stage was classified according to 7th AJCC/UICC staging system. T and N classifications did not differ, but Stage III was more frequent in the total thyroidectomy group probably because it included many elderly patients.

Table 1 Baseline clinicopathologic characteristics of the cohort with papillary thyroid carcinoma with minimal extrathyroidal extension ($N=255$)

	Total thyroidectomy ($N=173$) No. of patients (%)	Hemithyroidectomy ($N=82$) No. of patients (%)	p value
Sex (F:M)	145: 28	56: 26	< 0.001
Age (years)	50.4 ± 12.7	44.6 ± 11.8	0.001
Tumor size (mm)	12.0 ± 6.9	7.0 ± 3.7	< 0.001
Multiplicity	21 (12.1%)	9 (11.0%)	0.788
Lymphovascular invasion	17 (9.8%)	10 (12.2%)	0.566
T classification (T1/T2/T3/T4)	0/0/173/0	0/0/82/0	1.0
N classification (N0/N1a)	113/60	60/23	0.265
Stage (I/II/III/IV)	53/0/120/0	40/0/42/0	0.005
CND	145 (83.8%)	74 (90.2%)	0.168
Complication			
Hematoma	1 (0.6%)	0	1.0
Seroma	49 (28.3%)	22 (26.8%)	0.804
Transient hypoparathyroidism	65 (37.6%)	6 (7.3%)	< 0.001
Permanent hypoparathyroidism	5 (2.9%)	0	0.179
Transient VCP	9 (5.2%)	2 (2.4%)	0.511
Permanent VCP	2 (1.6%)	0	1.0
RAI ablation	157 (90.8%)	0	< 0.001
Dose of RAI (mCi)	117.0 ± 36.6	0	
Follow-up (month)	66.7 ± 21.7	62.8 ± 24.7	0.199

CND central neck dissection, *VCP* vocal cord palsy, *RAI* radioactive iodine

Clinicopathologic characteristics of the propensity score-matched cohort

Sex, age, tumor characteristics such as tumor size, multiplicity, lymphovascular invasion, T and N classification, and Stage, and the rate of CND did not differ between the two groups in the PSM cohort (66 pairs of patient) (Table 2).

Postoperative complications

In terms of complications, transient hypoparathyroidism was significantly more common in the total thyroidectomy group while permanent hypoparathyroidism, recurrent laryngeal nerve palsy, hematoma and seroma did not differ between the groups. 61 (92.4%) of the total thyroidectomy patients received postoperative radioactive iodine (RAI) ablation with a mean dose of 119 mCi. The mean follow-up period was 70 months in the total thyroidectomy group and 62.4 months in the hemithyroidectomy group ($p=0.143$) (Table 2).

Recurrence and survival

There was no significant difference in recurrence rate between the two PSM groups (Table 3). All patients with recurrences were confirmed by FNAC, except one patient with lung metastasis. Two patients (3.0%) suffered recurrence in the total thyroidectomy group (1 in the central lymph node and the other in the lung), and one (1.5%) in the hemithyroidectomy group (in the central lymph node) ($p=1.0$). Recurrence rates also did not differ in the subgroups classified according to tumor size (1.8% vs. 1.8% in tumor size ≤ 10 mm group and 11.1% vs. 0% in tumor size 11–20 mm group, $p=1.0$ in both).

Recurrence-free survival curves did not differ between the two groups (Fig. 2). In the total thyroidectomy and hemithyroidectomy groups 10-year RFS was 96.5% and 97.9%, respectively ($p=0.899$). RFS also did not differ in the subgroup analysis according to tumor size (98.0% vs. 97.5% in tumors ≤ 10 mm, $p=0.719$ and 83.3% vs. 100% in tumors 11–20 mm, $p=0.414$).

We also divided the patients into two subgroups according to the presence of occult metastatic LN. In the propensity score-matched cohort, occult central LN metastasis was confirmed in 23 (53.5%) and 19 (39.6%) of the total thyroidectomy and hemithyroidectomy groups ($p=0.421$). The mean number of metastatic central LNs was 2.27 ± 2.77 (range 1–10) and 2.16 ± 2.22 (range 1–10) in the total thyroidectomy and hemithyroidectomy groups, respectively ($p=0.293$) (Table 2). Recurrence rate did not differ between the total thyroidectomy and hemithyroidectomy groups in both subgroup analysis (0% vs. 5.3% in the positive LN group, $p=1.0$ and 3.3% vs. 0% in the negative LN group, $p=0.504$). Recurrence-free survival curves also did not

Table 2 Clinicopathologic characteristics of the patient groups after propensity score matching ($N=132$)

	Total thyroidectomy ($N=66$) No. of patients(%)	Hemithyroidectomy ($N=66$) No. of patients(%)	p value
Sex (F:M)	50:16	50:16	1.0
Age (years)	45.2 ± 11.0	44.6 ± 11.2	0.778
Tumor size (mm)	7.3 ± 3.1	7.2 ± 3.1	0.843
Multiplicity	8 (12.1%)	4 (6.1%)	0.365
Lymphovascular invasion	6 (9.1%)	4 (6.1%)	0.744
T classification (T1/T2/T3/T4)	0/0/66/0	0/0/66/0	1.0
N classification (N0/N1a)	43/23	48/19	0.421
Stage (I/II/III/IV)	28/0/38/0	33/0/33/0	0.383
CND	61 (92.4%)	58 (87.9%)	0.381
Unilateral	54 (81.8%)	58 (87.9%)	
Bilateral	7 (10.6%)	0	
Number of metastatic lymph node	2.27 ± 2.77	2.16 ± 2.22	0.293
Complication			
Hematoma	0	0	1.0
Seroma	25 (37.9%)	19 (28.8%)	0.268
Transient hypoparathyroidism	32 (48.5%)	5 (7.6%)	< 0.001
Permanent hypoparathyroidism	2 (3.0%)	0	0.496
Transient VCP	2 (3.0%)	1 (1.5%)	1.0
Permanent VCP	0	0	1.0
RAI ablation	61 (92.4%)	0	< 0.001
Dose of RAI(mCi)	119.0 ± 34.1	0	
Follow-up (month)	70.0 ± 21.5	62.4 ± 27.6	0.143

CND central neck dissection, *VCP* vocal cord palsy, *RAI* radioactive iodine

Table 3 Comparisons of recurrence rates in the subgroups according to tumor size

	Total			Tumor size (≤ 10 mm)			Tumor size (11–20 mm)		
	Total thyroidectomy ($N=66$) No. of patients (%)	Hemithyroidectomy ($N=66$) No. of patients (%)	p value	Total thyroidectomy ($N=57$) No. of patients (%)	Hemithyroidectomy ($N=57$) No. of patients (%)	p value	Total thyroidectomy ($N=9$) No. of patients (%)	Hemithyroidectomy ($N=9$) No. of patients (%)	p value
Follow-up (month)	70.0 ± 21.5	62.4 ± 27.6	0.143	69.9 ± 23.8	62.1 ± 26.9	0.108	70.2 ± 22.6	63.8 ± 22.7	0.531
Recurrence rate	2/66 (3.0%)	1/66 (1.5%)	1.0	1/57 (1.8%)	1/57 (1.8%)	1.0	1/9 (11.1%)	0	1.0

differ in both subgroup analysis ($p=0.602$ in the positive LN group and $p=0.373$ in the negative LN group).

Discussion

The prevalence of ETE is reported to range from 6 to 77% [1]. ETE is considered an important poor prognostic factor in PTC. It is associated with increased likelihood of central compartment lymph node metastasis and recurrence, and decreased survival [1–4]. The prognostic significance of ETE was initially evaluated only in terms of presence or absence, but in the last decade several authors distinguished microscopic or minimal ETE from gross or maximal ETE and observed that the degree of ETE correlated with tumor recurrence rate: PTC with minimal ETE has poorer outcomes than PTC without ETE, but better outcomes than PTC with maximal ETE [10–13].

Furthermore, some studies have found that minimal ETE was not related to poor prognosis [14–21]. According

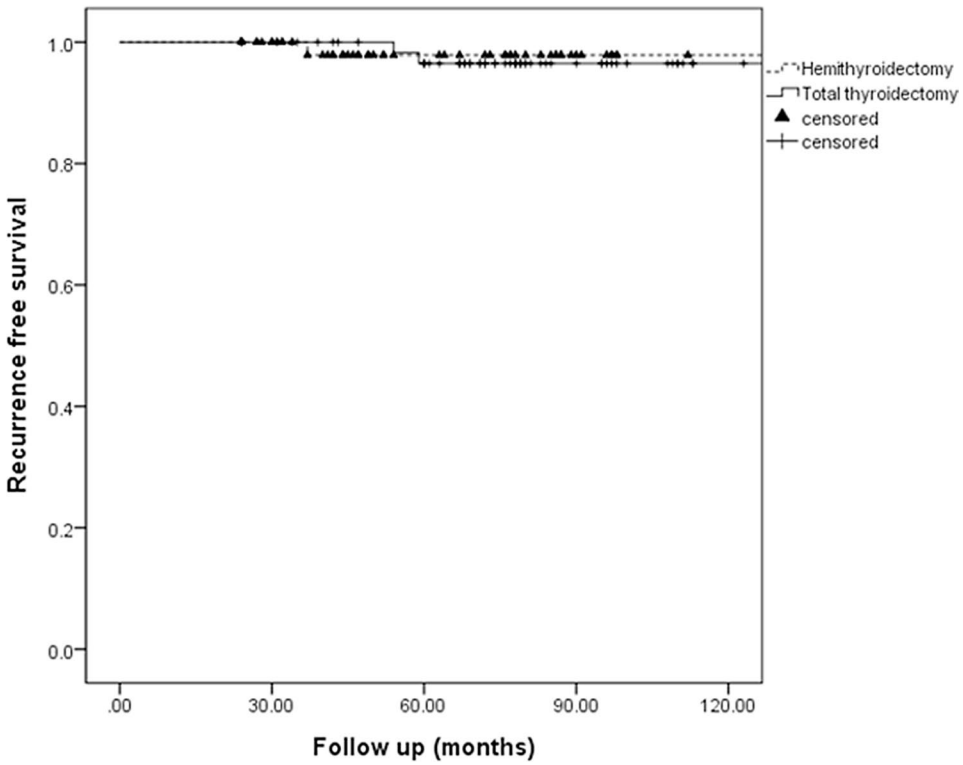

Fig. 2 Recurrence-free survival curves in the total thyroidectomy and hemithyroidectomy groups

to Memorial Sloan Kettering Cancer Center data, 10-year disease-specific survival and RFS were not different between patients with PTC < 4 cm with and without microscopic ETE [14]. In our previous study of 967 PTC patients we found that recurrence rate (3.3% vs. 2.5%) and 10-year disease-free survival (94.8% vs. 96.5%) were not significantly different between PTC patients without and with minimal ETE although central or lateral lymph node metastasis was more frequent in cases with minimal ETE [15].

Minimal ETE has been distinguished from maximal ETE in various staging systems. Minimal ETE, including microscopic perithyroidal ETE and strap muscles invasion, was separated from gross ETE and downstaged to T3 in the AJCC cancer staging system, since the 6th edition [22]. The ATA also recommended differentiating minor extrathyroidal extension (ATA intermediate risk) from gross extrathyroidal invasion of surrounding structures (ATA high-risk) [27]. Furthermore, in the revised staging system of the 8th edition, gross invasion to only strap muscles is classified as T3b, and minimal ETE is not included in the T classification criteria [9]. In this study, TNM stage was classified according to the 7th AJCC staging system in that minimal ETE was classified as T3. Also, all patients were treated before 2017 when the 8th edition of AJCC was revised.

In terms of extent of thyroidectomy, total thyroidectomy has been considered the primary initial surgical treatment option for PTC > 4 cm, maximal ETE and clinically apparent lymph node metastasis [27–30]. Lobectomy is recommended in cN0 PTC < 1 cm without ETE. For cN0 PTC 1–4 cm without ETE, initial surgery can be either total thyroidectomy or lobectomy. However, there is currently no consensus for PTC < 4 cm with minimal ETE.

Recent studies have indicated that the oncologic outcomes of unilateral thyroid resection are equivalent to those of total thyroidectomy in selected cases of PTC [23–26]. In one study of 5432 PTC patients (4612 total thyroidectomies and 820 lobectomies) using the SEER database 10-year overall survival after partial thyroidectomy did not differ from total thyroidectomy in both the low-risk group (89% after total thyroidectomy vs. 91% after partial thyroidectomy) and the high-risk group (72% after total thyroidectomy vs. 78% after partial thyroidectomy), when risk was stratified by the AMES classification system. Interestingly, in that study, the partial thyroidectomy group included patients with ETE (6.7%), tumor size ≥ 5 cm (5.2%) and regional lymph node metastases (9.8%) [25].

In view of those favorable oncologic outcomes of minimal ETE and lobectomy, we considered that hemithyroidectomy might be suitable for PTC < 4 cm with minimal ETE. Therefore, we performed this study to carefully evaluate the oncologic outcomes of hemithyroidectomy in cN0 PTC < 4 cm with minimal ETE using propensity score matching to reduce selection bias. However, in this study, we could only analyze the oncologic outcomes of hemithyroidectomy in PTC ≤ 2 cm with minimal perithyroidal ETE

because very few patients with PTCs of 2–4 cm or with sternothyroid muscle invasion underwent hemithyroidectomy.

To the best of our knowledge, this is the first study to compare oncologic outcomes between total thyroidectomy and hemithyroidectomy in patients with cN0 PTC ≤ 2 cm and minimal ETE. In this study, recurrence rates (3.0% vs. 1.5%, $p = 1.0$) and 10-year RFSs (96.5% vs. 97.9%, $p = 0.899$) did not differ between the total thyroidectomy group and the hemithyroidectomy group of patients PTC ≤ 2 cm. We also divided the patients into two subgroups of tumor sizes ≤ 10 mm and 11–20 mm, and there were again no differences in recurrence rates and 10-year RFS between the two subgroups. Furthermore, 92% of total thyroidectomy patients underwent postoperative RAI ablation. Nonetheless, the recurrence rate and 10-year RFS of the hemithyroidectomy group were similar to those of the total thyroidectomy group. This result further supports the conclusion that hemithyroidectomy is comparable to total thyroidectomy in patients with minimal ETE since postoperative RAI ablation can improve the prognosis of total thyroidectomy on its own.

In this study, we also performed the subgroup analysis according to the presence or absence of occult-positive LN. Recurrence rate and recurrence-free survival did not differ between the total thyroidectomy and hemithyroidectomy groups in both positive-LN and negative-LN subgroup. This result might support that hemithyroidectomy is comparable in oncologic outcome to total thyroidectomy for patients with cN0 PTC with minimal ETE and 2 cm or less in size regardless of occult central LN metastasis.

Ahn et al. investigated oncologic outcomes after hemithyroidectomy in cN0 PTC ≤ 1 cm and showed that for 262 patients without ETE and 86 patients with microscopic ETE, recurrence rates (4.2% vs. 7.0%, $p = 0.385$) and 5-year disease-specific survivals (94.7% vs. 92.7%, $p = 0.338$) were similar [17]. These data might support our finding that there was no significant difference between the effects of total thyroidectomy and hemithyroidectomy on recurrence rates and RFS in the subgroups of PTC of ≤ 1 cm with minimal ETE.

In terms of complications, total thyroidectomy was associated with a higher complication rate and higher morbidity than lobectomy even when performed by high-volume surgeons [33] and it also results in a requirement for life-long thyroid hormone supplementation. In our data, transient hypoparathyroidism was more frequent in the total thyroidectomy than the hemithyroidectomy group. Therefore, from the viewpoint of complications, hemithyroidectomy is preferable to total thyroidectomy for small low-risk PTCs.

This study has several limitations. First, it is a retrospective non-randomized study, which could be affected by selection bias although we conducted PSM analysis to reduce such bias. Second, we analyzed a relatively small number of patients because the number of patents who underwent hemithyroidectomy was limited; in the past decade, total thyroidectomy was generally preferred for PTC with ETE. Also, the majority of patients in the study were papillary microcarcinomas, and patients with tumors size 11–20 mm was only 14%. Therefore, caution is necessary when interpreting the results of the subgroup of tumor size 11–20 mm. Third, actually the recurrence rate is low in PTC. Therefore, a large number of cases is necessary to demonstrate small differences statistically. Also the follow-up period was relatively short considering the indolent natural course of PTC. Further prospective randomized studies with longer-term follow-up and large series of tumor size 11–20 mm or even larger between 11–40 mm with minimal ETE are necessary to overcome the limitations.

Conclusion

Based on the results of this study, hemithyroidectomy can be recommended for clinically node-negative PTC 1 cm or less with minimal ETE. Also it can be considered for clinically node-negative PTC 11–20 mm with minimal ETE although caution is necessary. Further studies of larger numbers of patients and with longer-term follow-up are needed to verify these results.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest pertaining to this manuscript.

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