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Prognostic value of tumor size and minimal extrathyroidal extension in papillary thyroid carcinoma

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ABSTRACT

Background: Tumour size and extrathyroidal extension (ETE) may impact papillary thyroid carcinoma (PTC) outcomes. We therefore examined the prognostic value of tumour size and ETE for predicting posttreatment recurrence in PTC patients.
Methods: A total of 2,902 patients who underwent thyroidectomy for previously untreated T1–T3 PTC (7th edition American Joint Committee on Cancer) at our tertiary referral center were included. Univariate and multivariate Cox proportional hazard regression analyses were used to determine significant factors predictive of posttreatment recurrence-free survival (RFS).
Results: In univariate analysis, tumour factors (including tumour size, multifocality, ETE, and lymphovascular invasion), nodal factors (including positive lymph node number, lymph node ratio, and extranodal extension), and MACIS (metastases, age, completeness of resection, invasion, and size) scores were significantly associated with RFS outcomes ($P < 0.001$). In multivariate analysis, tumour size >4 cm ($P < 0.001$) and multifocality ($P = 0.038$) were the independent factors of RFS. Nodal factors and MACIS scores were also independent factors of RFS.
Conclusion: Tumour size impacts RFS after thyroidectomy in T1–T3 PTC patients.

Introduction

Papillary thyroid carcinoma (PTC) is a major subtype of thyroid carcinomas and has very low disease-specific mortality.[1–3] PTC has rapidly increased in incidence because of early detection using high-resolution ultrasonography and surveillance techniques.[3,4] Fortunately, PTC is a highly treatable disease with excellent outcomes of >90% overall survival rate at long-term follow-up of 20–30 years after total or near-total thyroidectomy.[5] However, the overall survival of PTC differs according to age, tumor size, local invasion, regional metastasis, or distant site metastasis.[2,6,7] Despite its indolent clinical nature, cancer-specific mortality for advanced-stage PTC has increased with the annual 3% overall incidence increase in the US.[8] Survival is generally predicted by the tumor-node-metastasis (TNM) staging system proposed by the American Joint Committee on Cancer (AJCC). The TNM staging system (8th edition) for differentiated thyroid cancer has recently been updated with significant changes including that minor extrathyroidal extension (ETE) was removed from the T3 classification.[7] A risk stratification system for recurrence has also been proposed by the American Thyroid Association (ATA).[9] Despite very low mortality from PTC, posttreatment recurrence of PTC is relatively common in locoregional and distant sites,[2] which may significantly impact the quality of life of PTC patients.

Macroscopic ETE is associated with a higher rate of disease recurrence compared with microscopic ETE.[10] The extent of ETE—categorized as microscopic (now classified as T1), macroscopic (T3b, gross ETE invading only strap muscles), and macroscopic maximal (T4a/b, gross ETE invading anything other than strap muscles) invasion—might increase with tumor size, showing different posttreatment recurrence rates and predictiveness of nodal metastasis.[11,12] The prognostic significance of microscopic ETE is controversial.[10] However, microscopic ETE is associated with lower recurrence-free survival (RFS) outcomes compared with no ETE.[13] Papillary thyroid microcarcinoma with microscopic ETE

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Table 1
Patient characteristics ($N = 2,902$).

Variable	*N*	%
Age (y), median (IQR)	51 (43–58)	
Sex		
Male	619 (21.3)	
Female	2,283 (78.7)	
Smoking	388 (13.4)	
Tumour size (cm), median (IQR)	1.1 (0.7–1.4)	
Tumour multifocality		
Multifocal	962	33.1
Bilateral ($n = 2,533$)[a]	618	24.4
Extrathyroidal extension		
No	1,191	41.0
Microscopic	1,382	47.6
Macroscopic	329	11.3
Lymphovascular invasion	227	7.8
pTNM stage		
T1a/T1b/2/3 (7th edition)	917/207/62/1,716	31.6/7.1/2.1/59.1
T1a/T1b/2/3 (8th edition)	1,707/620/227/348	58.8/21.4/7.8/12.0
N0/N1a/N1b (7th and 8th editions)	1,319/1,141/442	45.5/39.3/15.2
Overall I/II/III/IV (7th edition)	1,334/18/1,272/278	46.0/0.6/43.8/9.6
Overall I/II (8th edition)	2,339/563	80.6/19.4
Treatment		
Lobectomy/total thyroidectomy plus CND	369/2,533	12.7/87.3
Lateral neck dissection	459	15.8
Postoperative RAI	2,325	80.1
Follow-up information		
Duration (months), median (IQR)	89 (64–124)	
Last status, NED/DOD/DOC/AD	2,831/5/40/26	97.6/0.2/1.4/0.9
Recurrence, any site	133	4.6

Abbreviations: AD; alive with disease; CND, unilateral or bilateral central neck dissection (level VI); DOC, died of other cause; DOD, died of disease; IQR, interquartile range; LN, cervical lymph node; NED, no evidence of disease; pTNM, pathological tumour-node-metastasis stage proposed by the American Joint Committee on Cancer; RAI, radioactive iodine.
[a] Calculated in the patients who underwent total thyroidectomy.

might be treated aggressively when co-presenting with cervical lymph node metastasis (N1).[14] Reflecting the recent changes in the TNM staging system, the prognostic significance of ETE needs to be further examined in T1–T3 PTC patients. Tumor size and ETE have served as the main factors in the tumor (T) classification of the AJCC TNM staging manual.[6,7] Therefore, we examined the prognostic value of tumor size and minimal ETE for predicting posttreatment recurrence in pathological T1–T3 PTC patients.

Patients and methods

Study patients

Electronic records were carefully reviewed for patients who underwent thyroidectomy with previously untreated T1–T3 PTC in the Department of Otolaryngology at Asan Medical Center between March 2006 and December 2015. The tumors were pathologically staged according to the 7th and 8th editions of the AJCC TNM staging manual.[6,7] Exclusion criteria were patients with T4 classification or distant metastases initially, referral patients with recurrent PTC, patients with a history of previous neck dissection or irradiation, and patients who were lost to follow-up within 2 years. This study was reviewed and approved by our Institutional Review Board, and the informed consent requirement for each patient was waived.

The patients underwent thyroid lobectomy or total thyroidectomy depending on tumor size, ETE, and lymph node involvement. Total thyroidectomy was more likely recommended even for small size tumors according to the recommendation of the ATA management guidelines (previous version, 2009).[15] The patients also underwent unilateral or bilateral central neck LN dissection regardless of the presence of clinical LN metastasis according to our institutional protocol. The patients with clinical LN metastasis to the lateral neck underwent simultaneous lateral neck LN dissection of levels I–V or II–VI. The tumor and neck dissection samples were sent for pathological examination. Endoscopic or robotic procedures were not used to remove tumors or for LN dissections.[16] Pathological tumor size, multifocality, bilaterality, ETE, and lymphovascular invasion were reported for each patient. From neck dissection samples, the number of LNs examined and involved, as well as extranodal extension, was reported. The patients received postoperative adjuvant radioactive iodine (^{131}I) (RAI) ablation therapy of 30–150 mCi according to the indications of the previous ATA management guidelines.[15]

The patients were regularly followed at the outpatient clinic every 3–6 months in the first year, and annually thereafter. Serum thyroglobulin (Tg), anti-Tg, free thyroxine, and thyroxine-stimulating hormone concentrations were measured at the outpatient visits. Chest radiography and high-resolution ultrasonography were checked annually. Any lesions suspicious for recurrence were assessed with specific imaging workups with biopsies.[17] For endpoint analyses, posttreatment recurrence was defined as structural recurrence identified using imaging modalities followed by histological confirmation, regardless of serum Tg concentrations.[9,18] Patients with recurrence underwent salvage surgery for loco-regional disease, and palliative treatment for distant site disease.

Variables

Variables included age (<55 years versus ≥55 years), sex, tumor size (≤2 cm versus 2.1–4 cm versus >4 cm), multifocality, bilaterality, ETE ("no" versus "microscopic" versus "macroscopic"), lymphovascular invasion, pathological tumor (pT) and

nodal (pN) classifications, overall TNM stage, extent of thyroidectomy (lobectomy versus total thyroidectomy), number of LNs examined (≤20 versus >20), number of positive LNs (≤5 versus >5), LN ratio (≤0.25 versus >0.25), extranodal extension, MACIS (distant metastasis-age-invasion into surrounding area-completeness of resection-size of tumor) score (<6 versus ≥6), and postoperative RAI. Tumor size was determined during pathological examination, and microscopic or macroscopic ETE were assessed from operative and pathological examinations. LN ratio was calculated as the number of positive LNs divided by the total number of LNs examined.[19]

Statistical analysis

Continuous variables were expressed as medians and interquartile ranges (IQR) or means and standard deviations (for mean comparison among different groups). Categorical variables were expressed as numbers and percentages. The characteristics of no ETE, microscopic ETE, and macroscopic ETE were compared using χ^2 exact test for categorical variables and Kruskal-Wallis test for continuous variables, with Bonferroni-adjusted post-hoc test. The primary endpoint of interest was RFS. The time point for RFS was measured from the day of surgery to either recurrence (at any site) or most recent follow-up. The cutoff values for the optimal number of examined and positive LNs as well as LN ratio were determined using time-dependent receiver operating characteristics (ROC) curve analyses and area under the ROC curve (AUC) estimates associated with RFS outcomes.[20] Univariate Cox proportional hazard regression analyses were used to define significant factors for RFS. Multivariate Cox proportional hazard regression analyses were used to find the independent factors predictive of RFS with the backward elimination of variables with $P < 0.1$ on univariate analyses. Variables with multi-collinearity were separately fit.[21] Hazard ratios (HR) and 95% confidence intervals (CI) were estimated. Kaplan-Meier and log-rank tests were used to determine survival and statistical significance, respectively. A *P*-value less than 0.05 was considered to indicate the statistical significance and all statistical tests were two-tailed. The statistical analyses were performed using the IBM® SPSS® Statistics version 24.0 for Windows (IBM Corp., Armonk, NY).

Results

Patient characteristics

A total of 2,902 patients were included in this study after excluding 628 patients, cconsisting of 619 (21.3%) men and 2,283 (78.7%) women, with a median age of 51 years (IQR 43–58 years) (Table 1). Median tumor size was 1.1 cm (IQR 0.7–1.4 cm). Tumors with sizes of ≤2 cm, 2.1–4 cm, and >4 cm were found in 2,517 (86.7%), 323 (11.1%), and 62 (2.1%) patients, respectively. Tumor multifocality was found in 962 (33.3%) patients, and bilaterality was found in 618 (24.4%) of 2,533 patients who underwent total thyroidectomy. Microscopic and macroscopic ETE was found in 1,382 (47.6%) and 329 (11.3%) patients, respectively. The tumors were pathologically staged as T1 in 1,124 (38.7%) patients, T2 in 62 (2.1%) patients, and T3 in 1,716 (59.1%) patients (AJCC 7th edition). Pathological LN positivity was found in 1,583 (54.5%) patients, including in the central neck compartment in 1,517 (52.3%) patients and in the lateral neck compartment in 431 (14.9%) patients. Median numbers of LNs examined and involved were 9[6–16] and 1 (0–3), respectively. The median LN ratio was 0.071 (0–0.265). Pathological extranodal extension was found in 373 (12.9%) patients. Median MACIS score was 4.8 (4.2–5.6). Median follow-up period was 89 months (64–124 months). At the last follow-up, 2,831 (97.6%) patients were alive with no evidence of disease, only five (0.2%) died of disease, 40 (1.4%) died of other causes, and 26 patients were alive with disease. Therefore, we did not calculate overall or disease-specific survivals because of the lack of significant numbers of events. During the follow-up, recurrence in any site was found in 133 (4.6%) patients, including in remnant thyroid gland in 3 (0.1%) patients who underwent lobectomy, thyroidectomy bed or central neck LNs in 51 (1.7%) patients, lateral neck LNs in 85 (2.9%) patients, and distant sites in 17 (0.6%) patients, with some patients overlapping in recurrent sites. The 5- and 10-year RFS rates of all patients were 95.9% (95% CI 95.5–96.3%) and 95.0% (94.5–95.5%), respectively.

Comparison of characteristics according to the extent of ETE

Age at disease presentation was higher in patients with microscopic ETE compared with those with no or macroscopic ETE ($P < 0.001$) (Table 2). Tumors in patients with ETE were larger than in

Table 2
Comparison of characteristics among patients with no ETE, microscopic ETE, and macroscopic ETE in T1–T3 papillary thyroid carcinoma tumors.

Variable	No ETE (n = 1,191)	Microscopic ETE (n = 1,382)	Macroscopic ETE (n = 329)	P[a]
Age (y), mean (SD)	49.9 (11.2)	51.6 (12.0)	49.4 (13.7)	<0.001
Sex, male	272 (22.8)	270 (19.5)	77 (23.4)	0.078
Tumour size (mm), mean (SD)	8.8 (0.7)	11.5 (8.0)	19.6 (15.0)	<0.001
Multifocality	318 (26.7)	500 (36.2)	144 (43.8)	<0.001
Bilaterality (n = 2533)	194 (20.5)	323 (25.6)	101 (31.0)	<0.001
Lymphovascular invasion	49 (4.1)	129 (9.3)	49 (14.9)	<0.001
Nodal positivity	512 (43.0)	807 (58.4)	264 (80.2)	<0.001
Central neck	496 (41.6)	774 (56.0)	247 (75.1)	<0.001
Lateral neck	91 (7.6)	201 (14.5)	139 (42.2)	<0.001
No. of LNs examined, mean (SD)	12.5 (13.7)	15.1 (17.6)	29.2 (27.3)	<0.001
No. of LNs involved, mean (SD)	1.6 (3.1)	2.9 (4.7)	6.6 (8.2)	<0.001
LN ratio, mean (SD)	0.124 (0.206)	0.191 (0.242)	0.234 (0.222)	<0.001
ENE	86 (7.2)	184 (13.3)	103 (31.3)	<0.001
MACIS score, mean (SD)	4.4 (0.8)	5.1 (0.9)	5.8 (1.2)	<0.001
Death, any causes	12 (1.0)	27 (2.0)	6 (1.8)	0.140
Recurrence, any site	25 (2.1)	78 (5.6)	30 (9.1)	<0.001

Note: Variables are expressed as numbers (percentages) unless indicated otherwise.
Abbreviations: CND; central neck dissection; ENE, extranodal extension; ETE, extrathyroidal extension; LN, cervical lymph node; MACIS, distant metastasis-age-invasion into surrounding area-completeness of resection-size of tumour; SD, standard deviation.
[a] The χ^2 exact test for categorical variables; Kruskal-Wallis test for continuous variables, $P < 0.05$.

Table 3
Univariate analyses of clinicopathological factors affecting recurrence-free survival.

			Recurrence-free survival		
Variable	*N* (%)	5-y rate (95% CI)	HR	95% CI	*P*
Age					
<55 year	1,805 (62.2)	96.0 (95.5–96.5)	1		
≥55 years	1,097 (37.8)	95.8 (95.2–96.4)	1.05	0.74–1.49	0.787
Sex					
Female	2,283 (78.7)	96.6 (96.2–97.0)	1		
Male	619 (21.3)	93.3 (92.3–94.3)	2.03	1.42–2.91	<0.001
Size of tumour					
≤2 cm	2,517 (86.7)	97.0 (96.7–97.3)	1		<0.001
2.1–4 cm	323 (11.1)	91.7 (9.01–9.33)	2.93	1.95–4.40	<0.001
>4 cm	62 (2.1)	77.4 (72.1–82.7)	9.27	5.50–15.62	<0.001
Multifocality					
No	1,940 (66.9)	97.1 (96.7–97.5)	1		
Yes	962 (33.3)	93.6 (92.8–94.4)	2.10	1.49–2.94	<0.001
Bilaterality (n = 2,533)					
No	1,915 (75.6)	95.7 (95.2–96.2)	1		
Yes	618 (24.4)	95.1 (94.2–97.0)	1.24	0.84–1.83	0.274
Extrathyroidal extension					
None	1,191 (41.0)	98.1 (97.7–98.5)	1		<0.001
Microscopic	1,382 (47.6)	95.1 (94.5–95.7)	2.65	1.69–4.15	<0.001
Macroscopic	329 (11.3)	91.6 (90.0–93.2)	4.53	2.66–7.70	<0.001
Lymphovascular invasion					
No	2,675 (92.2)	96.4 (96.0–96.8)	1		
Yes	227 (7.8)	90.7 (88.7–92.7)	2.78	1.77–4.36	<0.001
pT classification (7th edition)					
T1	1,124 (38.7)	98.1 (97.7–98.5)	1		<0.001
T2	62 (2.1)	98.4 (96.8–100)	0.74	0.10–5.50	0.743
T3	1,716 (59.1)	94.4 (93.8–95.0)	2.94	1.89–4.60	<0.001
pT classification (8th edition)					
T1	2,327 (80.2)	97.1 (96.7–97.5)	1		<0.001
T2	227 (7.8)	91.9 (90.1–93.7)	2.90	1.80–4.66	<0.001
T3	348 (12.0)	90.8 (89.2–92.4)	3.24	2.17–4.84	<0.001
pN classification					
N0	1,319 (45.5)	98.9 (98.6–99.2)	1		<0.001
N1a	1,141 (39.3)	96.1 (95.5–96.7)	3.39	1.96–5.88	<0.001
N1b	442 (15.2)	86.8 (85.2–88.4)	12.20	7.16–20.79	<0.001
Overall TNM stage (7th edition)					
I	1,334 (46.0)	97.1 (96.6–97.6)	1		<0.001
II	18 (0.6)	NE	NE		0.949
III	1,272 (43.8)	96.8 (96.3–97.3)	1.03	0.68–1.56	0.900
IV	278 (9.6)	86.0 (83.9–88.1)	4.88	3.21–7.41	<0.001
Overall TNM stage (8th edition)					
I	2,339 (80.6)	96.8 (96.4–97.2)	1		
II	563 (19.4)	92.4 (91.3–93.5)	2.40	1.69–3.42	<0.001
Extent of thyroidectomy					
Lobectomy	369 (12.7)	98.5 (97.8–99.2)	1		
Total thyroidectomy	2,533 (87.3)	95.6 (95.2–96.0)	2.75	1.21–6.25	0.016
No. of LNs examined					
≤20	2,377 (81.9)	97.5 (97.2–97.8)	1		
>20	525 (18.1)	88.7 (87.3–91.1)	4.95	3.52–6.96	<0.001
No. of LNs involved					
≤5	2,426 (83.6)	98.1 (97.8–98.4)	1		
>5	476 (16.4)	85.0 (93.3–86.7)	8.45	5.96–11.96	<0.001
LN ratio					
≤0.25	2,162 (74.5)	97.8 (97.5–98.1)	1		
>0.25	740 (25.5)	90.4 (89.3–91.5)	4.10	2.91–5.79	<0.001
Extranodal extension					
No	2,529 (87.1)	97.6 (97.3–97.9)	1		
Yes	373 (12.9)	84.7 (82.8–86.6)	6.30	4.48–8.86	<0.001
MACIS score					
<6	2,487 (85.7)	96.8 (96.4–97.2)	1		
≥6	415 (14.3)	90.8 (89.4–92.2)	2.82	1.95–4.08	<0.001
Postoperative RAI					
No	577 (19.9)	98.7 (98.2–99.2)	1		
Yes	2,325 (80.1)	95.3 (94.9–95.7)	3.55	1.74–7.36	0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; LN, cervical lymph node; MACIS, distant metastasis-age-invasion into surrounding area-completeness of resection-size of tumour; NE, not estimated; pTNM, pathological tumour-node-metastasis stage proposed by the American Joint Committee on Cancer; RAI, radioactive iodine.

patients with no ETE, particularly for macroscopic ETE ($P < 0.001$). The presence of ETE was also associated with multifocality and bilaterality ($P < 0.001$). More positive LNs and higher LN ratios were more likely to be found in tumors with ETE compared with no ETE ($P < 0.001$). Extranodal extension was found more frequently in patients with ETE. MACIS scores were higher in patients with ETE. Post-thyroidectomy recurrence was more likely in patients with ETE. These findings were more predictive in patients with macroscopic ETE than

Table 4
Multivariate analyses of factors affecting recurrence-free survival.

	Recurrence-free survival		
Variable	HR	95% CI	*P*
Size of tumour			
≤2 cm	1		<0.001
2.1–4 cm	1.52	0.98–2.37	0.062
>4 cm	3.99	2.19–7.24	<0.001
Multifocality	1.46	1.02–2.07	0.038
Extrathyroidal extension			
None	1		0.174
Microscopic	1.12	0.61–2.04	0.714
Macroscopic	1.48	0.91–2.39	0.112
No. of positive LNs, >5	2.60	1.51–4.67	0.001
LN ratio, >0.25	1.77	1.15–2.73	0.009
Extranodal extension	1.82	1.20–2.76	0.005
MACIS score, ≥6	1.86	1.25–2.77	0.002

Abbreviations: CI, confidence interval; HR, hazard ratio; LN, cervical lymph node; MACIS, distant metastasis-age-invasion into surrounding area-completeness of resection-size of tumour.

microscopic ETE in the subgroup with ETE. However, overall mortality did not differ among patients with no ETE, microscopic ETE, and macroscopic ETE ($P = 0.140$).

Factors predictive of RFS

The numbers of LNs examined, numbers of LNs involved, and LN ratios were determined at cutoffs of 20, 5, and 0.25, respectively. Univariate analyses showed that age (≥55 years), sex (male), tumor size, multifocality, bilaterality, ETE, lymphovascular invasion, pT and pN classifications, overall TNM stage, extent of thyroidectomy, number of LNs examined and involved, LN ratio, extranodal extension, MACIS score, and postoperative RAI were significantly associated with RFS outcomes (all $P < 0.05$) (Table 3). Multivariate analyses showed that tumor size, multifocality, number of positive LNs, LN ratio, and MACIS score were the independent factors predictive of RFS (all $P < 0.05$) (Table 4). ETE was not independently associated with RFS outcomes ($P = 0.174$). Patients with tumors that were 2.1–4 cm and >4 cm had a 1.52-fold (95% CI 0.98–2.37) and 3.99-fold (2.19–7.24) increase in recurrence compared with those that were ≤2 cm. Fig. 1 shows the Kaplan-Meier curves estimating RFS according to tumor size and extent of ETE. Patients with tumors that were ≤2 cm, 2.1–4 cm, and >4 cm had 5-year RFS rates of 97.0% (95% CI 96.7–97.3%), 91.7% (9.01–9.33%), and 77.4% (72.1–82.7%), respectively ($P < 0.001$). The patients with no, microscopic, and macroscopic ETE showed only a modest decrease of 5-year RFS rates: 98.1% (97.7–98.5%), 95.1% (94.5–95.7%), and 91.6% (90.0–93.2%), respectively ($P < 0.001$).

Comments

The current study failed to show independent prognostic value of the presence of microscopic ETE or macroscopic ETE in predicting posttreatment recurrence in a large cohort of 2,902 T1–T3 PTC patients. Microscopic ETE was associated with larger tumors, multifocality, lymphovascular invasion, nodal positivity in both the central and lateral neck compartments, increased number of positive LNs, increased LN ratio, and extranodal extension compared with no ETE. In addition, adverse pathological tumor and nodal findings were more frequent in patients with macroscopic ETE compared with microscopic ETE. These data are supported by previous findings, which showed a close relationship between ETE and tumor size, nodal positivity, or extranodal extension in PTC.[11,12] The presence of ETE, even if minimal, might lead to a significantly higher incidence of extranodal extension, one of the worst pathological features prognostically.[22] Therefore, ETE was associated with increased overall recurrence rates of 2.6-fold in microscopic ETE and 4.5-fold in macroscopic ETE in our univariate analysis. However, in multivariate analysis, both microscopic and macroscopic ETE were not independent factors predictive of RFS.

The prognostic significance of ETE, particularly microscopic ETE, is still controversial. A previous study showed that microscopic ETE was significantly associated with lower 5-year RFS rates compared with no ETE, but was higher than macroscopic ETE.[13] A recent study also showed a strong association between microscopic ETE and other adverse prognostic factors and reduced RFS in the subgroup of PTC patients ≥55 years old.[23] The presence of microscopic ETE might impact recurrence, which has driven efforts for precise detection of ETE and individualization of surgical extent based on ETE detection.[24–26] However, no microscopic ETE, but only macroscopic ETE, has been shown to be correlated with poor oncological outcomes.[10,27] Microscopic ETE can be observed in papillary thyroid microcarcinoma, but is not associated with an increased risk of recurrence.[28] In addition, the previous study including all T1–T4 tumors also showed that only the massive macroscopic ETE (T4) but no microscopic (T1) or macroscopic (T3b) ETE were the independent factor of RFS.[12] This fact provided the basis of major changes in the T staging system (the AJCC 8th edition) by removing minor histological ETE from T3 classification (the AJCC 7th edition).[6,7] T3 was also subgrouped into T3a in the case of tumor size >4 cm and T3b in the case of gross ETE.[7] The changes provided better predictability of cancer progression and overall survival in patients with differentiated thyroid cancer.[29–32]

A recent study showed that tumor size, but not presence of microscopic or macroscopic ETE, was the independent factor predictive of RFS, locoregional failure, and distant site failure in differentiated thyroid cancer.[33] The study included 2,323

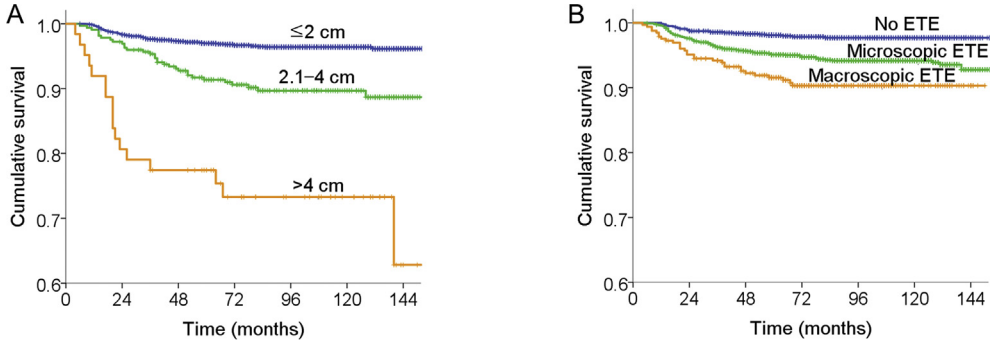

Fig. 1. Kaplan-Meier curves estimating recurrence-free survival according to tumor size (A) and extent of extrathyroidal extension (ETE, B) in T1–T3 PTC patients. Log-rank test, $P < 0.001$.

consecutive patients with T1–T3 differentiated thyroid cancer (defined per the AJCC 7th edition). The 5-year RFS was significantly lower in tumors >4 cm, regardless of the presence of ETE, thereby leading to the conclusion that tumor size, but not ETE, was an independent predictor for posttreatment recurrence. This conclusion may be implied from similar findings in our current study; however, that study showed more heterogeneity in terms of surgical extent, including tumor resections and central neck dissections, compared with the present study.

Tumor size has been recognized as the most important prognostic factor for differentiated thyroid cancer. A previous study showed that tumors >2 cm were associated with worse RFS and cancer-specific survival in combination with N classification.[34] Tumor size >2 cm was also the strongest factor predictive of cervical LN metastasis and recurrence, suggesting careful LN dissection for PTC with a large size.[35] The size of the tumor might be an important predictor for RFS, even in patients with clinically early-stage PTC ≤4 cm.[36] The prognostic impact of tumor size might be modified by patient age at diagnosis: no impact in patients aged <55 versus an independent predictor of RFS in patients aged ≥55 years.[37] The optimal threshold for RFS in this subgroup was 2 cm, and further stratification of tumor size did not improve the prognostic value.[37] The present study showed that tumors >2 cm were associated with lower RFS than those ≤2 cm. However, in multivariate analysis, tumors >2 cm but ≤4 cm were not independently associated with RFS compared with tumors ≤2 cm, while size >4 cm remained an independent predictor of RFS. These findings are different from the previously discussed recent study,[37] and may be secondary to differences in criteria, numbers, and surgical extent of included patients. Completion thyroidectomy might be a safe option after thyroid lobectomy.[38] Higher thyroid-stimulating hormone level affects the risk of differentiated thyroid cancer, which might influence the decision of thyroidectomy and extent.[39] Our findings on tumor size provides a basis for the suggestions of the 2015 ATA management guidelines, which allow thyroid lobectomy for up to 4 cm tumor size.[9] Therefore, the present study might help to guide surgeons' decisions on the extent of surgery for PTC patients in efforts to reduce posttreatment recurrence. For the other independent factors in our multivariate analyses, we have chosen not to discuss them in detail to avoid focus away from the primary issues of tumor size and ETE.

In conclusion, the present study suggests that tumor size >4 cm is an independent predictive factor of RFS. The presence of ETE is significantly associated with adverse pathological tumor findings and nodal findings. In univariate analyses, tumor size and ETE were significantly associated with RFS, while in multivariate analysis, tumor size was the independent predictor of RFS. Our findings support recent revisions of ATA guidelines that advocate for de-escalated surgery, including thyroid lobectomy, in patients with differentiated thyroid carcinoma tumors up to 4 cm.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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