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Risk factors for posttreatment recurrence in patients with intermediate-risk papillary thyroid carcinoma

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ABSTRACT

Background: Papillary thyroid carcinoma (PTC) is generally associated with favorable outcomes; however, intermediate-risk requires further evaluation. We therefore examined risk factors for posttreatment recurrence in patients with intermediate-risk PTC.
Methods: This study involved 1782 patients who underwent thyroidectomy for intermediate-risk PTC. Univariate and multivariate Cox proportional hazard regression analyses were used to identify the significant factors predictive of posttreatment recurrence-free survival (RFS).
Results: Of intermediate-risk factors, univariate analyses showed that clinical and pathological cervical lymph node (LN) positivity (cN1 and pN1), aggressive histology, and multifocality with microscopic extrathyroidal extension were significantly associated with RFS outcomes (all $P < 0.05$). In multivariate analyses, cN1, >5 pN1, and posttreatment radioactive iodine (RAI)-avid metastatic foci of intermediate risk remained the independent factors predictive of RFS (all $P < 0.05$). The combination of any three or more of these intermediate-risk factors appeared to increase the posttreatment recurrence rate.
Conclusion: Clinical nodal positivity, the number of positive LNs, and the presence of RAI-avid metastatic foci in the ATA intermediate-risk category might independently decrease RFS in patients with intermediate-risk PTC.

Papillary thyroid carcinoma (PTC) is the major pathology of thyroid malignancy related to relatively indolent clinical course and very low disease-specific mortality.[1–3] PTC is the most treatable disease, with excellent overall survival (OS) rates of >90% at 20–30 years posttreatment.[4] The survival of PTC patients differs according to their age, tumor size and local invasion, and regional or distant site metastasis.[2,5,6] Despite excellent survival outcomes, PTCs frequently spread to regional lymph nodes (LNs) and occasionally to remote organs at presentation.[7–9] This might contribute to the increased cancer-specific mortality for advanced-stage PTC along with an annual 3% increase in overall incidence in the US.[10] Prognostic prediction for cancer patient survival is generally proposed by the tumor-node-metastasis (TNM) staging manual of the American Joint Committee on Cancer (AJCC). The recent (8th edition) AJCC TNM staging for differentiated thyroid cancer is greatly changed from the previous 7th edition.[5,6] In terms of recurrence, a risk stratification system has also been proposed in the American Thyroid Association (ATA) management guidelines.[11,12] Despite very low mortality, PTC might involve the possibility of posttreatment recurrence developing in locoregional and distant sites,[2,13] which might impact patient quality of life.[14]

The ATA risk stratification system for recurrence consists of low, intermediate, and high risks.[11,12] Several factors have been added into the risk stratification system, which appeared to improve the discrimination ability and predictability of posttreatment recurrence.[15,16] The intermediate risk in the original 2009 ATA system included[1] microscopic tumor invasion to the perithyroidal soft tissues,[2] radioactive iodine (RAI)-avid metastatic foci in the neck detected on the first posttreatment whole-body RAI scan,[3] aggressive histology, and[4] PTC with

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lymphovascular invasion.[11] The 2015 ATA risk stratification added the risk factors of[5] clinical node positivity (cN1) or[6] pathological N1 with >5 LNs (all involved LNs <3 cm in largest dimension), and[7] multifocal papillary microcarcinoma with ETE and *BRAF*^{V600E} mutation (if known).[12]

The ATA intermediate-risk categories comprise a wide range of AJCC TNM stages (from T1N0 to T3N1 b), varied biological aggressiveness categories, and potentially different posttreatment clinical courses. A recent study examined the risk factors for early recurrence in patients with intermediate-risk PTC and excellent response to initial therapy.[17] Although the ATA management guidelines propose risk groups for recurrence,[11,12] the intermediate-risk group requires further evaluation. Therefore, this study examined risk factors for posttreatment recurrence in patients with intermediate-risk PTC.

Patients and methods

Study patients

Electronic records were reviewed to identify patients with previously untreated PTC who underwent thyroidectomy. The inclusion criteria were patients with intermediate-risk PTC according to the 2015 ATA management guidelines[12] who underwent thyroidectomy at the Department of Otolaryngology of our tertiary referral center between March 2006 and December 2015. The exclusion criteria were patients with ATA low- or high-risk PTC, referral patients with recurrent PTC, a history of previous neck dissection or irradiation, and early loss to follow-up within 2 years. The patients received PTC diagnoses based on high resolution ultrasonography-guided fine needle aspiration biopsy prior to surgery. This study was approved by the Institutional Review Board and the requirement for patient informed consent was waived.

The primary tumors were completely removed by lobectomy or total thyroidectomy depending on tumor size, extrathyroidal extension (ETE), and LN involvement. Total thyroidectomy was more likely recommended even in cases with small size tumor according to the 2009 American Thyroid Association management guidelines.[11] The patients also underwent unilateral or bilateral central neck LN dissection regardless of the presence of clinical LN metastasis, according to our institutional protocol. Patients with clinical LN metastasis to the lateral neck underwent simultaneous lateral neck LN dissection of levels I–V or II–IV. Endoscopic or robotic procedures were not used to remove tumors or lymph nodes.[18] Tumor and neck dissection samples were sent for pathological examination. Pathological tumor size, multifocality, ETE, lymphovascular invasion, number of LNs examined and involved, and extranodal extension were reported for each patient. The patients received postoperative adjuvant radioactive iodine (^{131}I) (RAI) ablation therapy of 30–150 mCi according to the indications from the previous ATA management guidelines.[11]

The patients were regularly followed up at an outpatient clinic at 3–6-month intervals during the first year and annually thereafter. Neck ultrasonography, chest radiography, whole-body iodine scanning, and serum thyroid function test were also performed at the follow-ups. Any recurrent or new lesions were identified by examinations or imaging and confirmed by biopsy.[19] For the endpoint analyses, structural recurrence was considered a posttreatment recurrence that was identified using imaging modalities followed by histological confirmation, regardless of serum thyroglobulin concentrations.[12,20] Additional surgery was performed in patients with structural recurrence, RAI therapy in patients with unresectable or distant metastatic diseases, and tyrosine kinase inhibitor were administered to patients with iodine-refractory diseases.[12,21]

Variables

The clinical data included patient age at diagnosis (<55 vs. ≥55 years), sex, cN1, and postoperative RAI therapy. The pathology data included tumor size (≤2 vs. 2.1–4 vs. >4 cm), lymphovascular invasion and ETE (no vs. microscopic), multifocality (with ETE), pathological tumor (pT) and nodal (pN) classifications, overall TNM stage, extent of thyroidectomy (lobectomy vs. total thyroidectomy), number of LNs examined (≤20 vs. >20), number of positive LNs (≤5 vs. >5), LN ratio (≤0.25 vs. >0.25), extranodal extension, and MACIS (distant metastasis-age-invasion into surrounding area-completeness of resection-size of tumor) score (<6 vs. ≥6). Tumor size, minimal ETE, multifocality, and LN number and size were determined on pathological examination. The LN ratio was the number of positive LNs divided by the number of LNs examined.[22] The tumors were pathologically staged according to the AJCC TNM staging manual (7th and 8th editions).[5,6]

Statistical analysis

Continuous variables were expressed as medians and interquartile ranges (IQRs), while categorical variables were expressed as numbers and percentages. The primary endpoints of interest were recurrence-free survival (RFS), defined as the time from the initial surgery to any-site recurrence or the last follow-up. The cutoff values for the optimal numbers of examined and positive LNs or LN ratio were determined using previously indicated values (12) and time-dependent receiver operating characteristics (ROC) curve analyses and areas under the ROC curve (AUC) estimates.[23] Univariate Cox proportional hazard regression analyses were used to identify the significant factors for RFS. Multivariate Cox proportional hazard regression analyses were used to determine the independent factors predictive of RFS with the backward elimination of the variables with $P < 0.1$ in univariate analyses. Variables with multi-collinearity were fit separately.[24] Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. Kaplan-Meier and log-rank tests were used to determine survival and statistical significance, respectively. Two-sided *P*-values <0.05 were considered significant. Statistical analyses were performed using IBM® SPSS® Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY).

Results

Patient characteristics

This study included a total of 1782 patients comprising 356 (20.0%) men and 1426 (80.0%) women with a median age of 51 years (IQR 44–59 years) (Table 1). The median tumor size was 1.1 cm (IQR 0.7–1.4 cm). Tumor multifocality was observed in 786 (44.1%) patients, while microscopic ETE was found in 1332 (74.7%) patients. Tumor aggressive variants of tall cell, columnar, or solid types were found in 44 (4.6%) patients. Lymphovascular invasion was detected in 158 (8.9%) patients. cN1 was observed in 431 (24.2) patients. T1 pathological tumor stage was found in 1569 (88.0%) patients, T2 in 198 (11.1%) patients, and T3 in 15 (0.8%) patients (AJCC 8th edition). Pathological LN positivity was found in 1039 (58.3%) patients, including in the central neck compartment in 991 (55.6%) patients and in the lateral neck compartment in 253 (14.2%) patients. A median of 10 (IQR 6–16) and 1 (0–4) LNs were examined and involved, respectively. The median LN ratio was 0.091 (IQR 0–0.300). Microscopic extranodal extension was found in 206 (11.6%) patients. The median MACIS score was 4.9 (IQR 4.3–5.6). The median follow-up period was 96 months (IQR 67–127 months). At the last follow-up, 1746 (98.0%) patients were alive with no evidence of disease, two (0.1%) had died of disease, 25

Table 1
Characteristics of patients with ATA intermediate risk (N = 1782).

Variable	*N*	%
Age (y), median (IQR)	51 (44–59)	
Sex		
Male	356	20.0
Female	1426	80.0
Tumor size (cm), median (IQR)	1.1 (0.7–1.4)	
Tumor multifocality	786	44.1
Aggressive histology	44	4.6
Microscopic extrathyroidal extension	1,332	74.7
Lymphovascular invasion	158	8.9
Clinical nodal positivity	431	24.2
Pathological nodal positivity	1039	58.3
Central neck	991	55.6
Lateral neck	253	14.2
No. of LNs examined, median (IQR)	10[6–16]	
No. of LNs involved, median (IQR)	1 (0–4)	
No. of positive LNs >5	309	17.3
pTNM stage		
T1a/T1b/2/3 (7th edition)	321/87/40/1334	18.0/4.9/2.2/74.9
T1a/T1b/2/3 (8th edition)	1093/476/198/15	61.3/26.7/11.1/0.8
N0/N1a/N1b (7th and 8th editions)	743/779/260	41.7/43.7/14.6
Overall I/III/IV (7th edition)	617/9/991/165	34.6/0.5/55.6/9.3
Overall I/II (8th edition)	1415/367	79.4/20.6
RAI-avid metastatic foci	47	2.6
Treatment		
Lobectomy plus CND/total thyroidectomy plus CND	155/1627	8.7/91.3
Lateral neck dissection	272	51.3
Postoperative RAI	1573	88.3
Follow-up information		
Duration (months), median (IQR)	96 (67–127)	
Last status, NED/DOD/DOC/AD	1746/2/25/9	98.0/0.1/1.4/0.5
Recurrence, any site	81	4.5

Abbreviations: AD; alive with disease; ATA, American Thyroid Association; CND, unilateral or bilateral central neck dissection; DOC, died of other cause; DOD, died of disease; IQR, interquartile range; LN, cervical lymph node; NED, no evidence of disease; pTNM, pathological tumor-node-metastasis stage proposed by the American Joint Committee on Cancer; RAI, radioactive iodine.

(1.4%) had died of other causes, and nine (0.5%) patients were alive with disease. Therefore, we did not calculate the overall or disease-specific survivals because of the lack of these events. During the follow-up, any-site recurrence was detected in 81 (4.5%) patients, including remnant thyroid gland in two (0.1%) patients with lobectomy, thyroidectomy bed or central neck LNs in 31 (1.8%) patients, lateral neck LNs in 59 (3.3%) patients, and distant sites in five (0.3%) patients, with overlapping recurrent sites in some patients. The five- and 10-year RFS rates of all study patients were 95.9% (95% CI 95.4–96.4%) and 94.9% (94.3–95.5%), respectively.

Factors predictive of RFS

The number of LNs examined and involved and LN ratio were determined at the cutoffs of 20, 5, and 0.25, respectively. Of the ATA intermediate-risk factors, cN1, >5 positive LNs, RAI-avid metastatic foci, aggressive histology, and multifocality with ETE were significantly associated with poor RFS outcomes (all $P < 0.05$) (Table 2). Among the other clinicopathological factors, male sex, larger tumor size, pathological T and N classifications, overall TNM stage, number of LNs examined (>20), LN ratio, microscopic extranodal extension, and MACIS score (≥6) were also significantly associated with poor RFS outcomes (all $P < 0.01$) (Table 2). In multivariate analyses, cN1, >5 positive LNs, and RAI-avid metastatic foci among the ATA intermediate-risk factors were independent factors predictive of RFS (all $P < 0.05$). LN ratio (>0.25), microscopic extranodal extension, and MACIS (≥6) score were independently associated with RFS (all $P < 0.05$). Fig. 1 shows the Kaplan-Meier curves estimating RFS according to the absence and presence of cN1, >5 positive LNs, and RAI-avid metastatic foci in the study patients. Patients with cN1, >5 positive LNs, or RAI-avid metastatic foci had an approximately 3.5-fold increased risk of posttreatment recurrence (Table 3). The combination of three or more ATA intermediate-risk factors was associated with significantly lower RFS outcomes than that in patients with one or two risk factors ($P < 0.001$, see Table 4 and Fig. S1).

Comments

The results of the present study revealed the risk factors in the ATA intermediate-risk category as well as other clinicopathological factors for the prediction of posttreatment recurrence in a large cohort of 1782 patients with intermediate-risk PTC. Of the 2015 ATA intermediate-risk factors, cN1, positive LNs >5, and the presence of posttreatment RAI-avid metastatic foci were the independent factors predictive of RFS. The other independent factors for recurrence were the LN ratio (>0.25), microscopic extranodal extension, and MACIS score (≥6). Microscopic ETE, multifocality with ETE, cN1, >5 positive LNs, lymphovascular invasion, RAI-avid foci, and aggressive histology were observed in 74.7%, 26.7%, 24.2%, 17.3%, 8.9%, 2.6%, and 1.9% of patients, respectively. The combination of any three or more intermediate-risk factors appeared to increase posttreatment recurrence rates. Our results might help to identify additional significant risk factors for intermediate risk and to stratify the risk groups to improve the prediction of posttreatment recurrence.

In the current study, posttreatment recurrence developed in 81 of 1782 (4.5%) intermediate-risk PTC patients, with a five-year recurrence rate of 4.1%. This was lower than the 25% recurrence rate in T4a PTC patients in a median of 77 months of follow-up[25] and higher than the 2.4% reported in early-stage low-risk PTC patients with a median of 83 months of follow-up.[26] The five-year RFS

Table 2
Univariate analyses of clinicopathological factors on recurrence-free survival.

Variable	*N* (%)	5-y rate (95% CI)	Recurrence-free survival		
			HR	95% CI	*P*
ATA intermediate risk factors					
Clinical nodal positivity					
No	1351 (75.8)	97.6 (97.2–98.0)	1		
Yes	431 (24.2)	90.7 (89.3–92.1)	4.56	2.93–7.09	<0.001
No. of positive LNs					
≤5	1473 (82.7)	97.8 (97.4–98.2)	1		
>5	309 (17.3)	86.9 (85.0–88.8)	6.91	4.45–10.75	<0.001
RAI-avid metastatic foci					
No	1735 (97.4)	96.1 (95.6–96.6)	1		
Yes	47 (2.6)	87.2 (82.3–92.1)	3.72	1.71–8.06	0.001
Aggressive histology					
No	1748 (98.1)	96.1 (95.6–96.6)	1		
Yes	34 (1.9)	88.2 (82.7–93.7)	2.75	1.01–7.53	0.048
Extrathyroidal extension					
No	450 (25.3)	96.8 (96.0–97.6)	1		
Microscopic	1332 (74.7)	95.6 (95.0–96.2)	1.45	1.83–2.54	0.197
Lymphovascular invasion					
No	1624 (91.1)	96.0 (95.5–96.5)	1		
Yes	158 (8.9)	94.5 (92.6–96.4)	1.41	0.71–2.83	0.328
Multifocality with ETE					
No	1307 (73.3)	96.8 (96.3–97.3)	1		
Yes	475 (26.7)	93.6 (92.5–94.7)	2.12	1.37–3.29	0.001
Other clinicopathological factors					
Age					
<55 years	1083 (60.8)	96.0 (95.4–96.6)	1		
≥55 years	699 (39.2)	95.8 (95.0–96.6)	1.03	0.66–1.61	0.893
Sex					
Female	1426 (80.0)	96.3 (95.8–96.8)	1		
Male	356 (20.0)	94.2 (92.9–95.5)	1.65	1.02–2.67	0.043
Tumor size					
≤2 cm	1569 (88.0)	96.7 (96.2–97.2)	1		
>2 cm but ≤4 cm	198 (11.1)	91.8 (89.8–93.8)	2.51	1.50–4.21	<0.001
>4 cm	15 (0.8)	80.0 (69.7–90.3)	5.44	1.71–17.36	0.004
pT classification (7th edition)					
T1	408 (22.9)	96.8 (95.9–97.7)	1		
T2	40 (2.2)	97.5 (95.0–100)	0.71	0.09–5.41	0.742
T3	1334 (74.9)	95.6 (95.0–96.2)	1.40	0.79–2.50	0.251
pT classification (8^h edition)					
T1	1569 (88.0)	96.7 (96.2–97.2)	1		
T2	198 (11.1)	91.2 (89.2–93.2)	2.51	1.50–4.21	<0.001
T3	15 (0.8)	80.0 (69.9–90.3)	5.44	1.71–17.36	0.004
pN classification (7th edition)					
N0	743 (41.7)	98.8 (98.4–99.2)	1		
N1a	779 (43.7)	95.1 (94.3–95.9)	4.45	2.17–9.14	<0.001
N1b	260 (14.6)	90.1 (88.2–92.0)	9.86	4.68–20.76	<0.001
Overall TNM stage (7th edition)					
I–II	626 (35.1)	97.0 (96.3–97.7)	1		
III	991 (55.6)	96.4 (95.8–97.0)	1.04	0.62–1.77	0.872
IV	165 (9.3)	88.9 (86.4–91.4)	3.64	2.00–6.61	<0.001
Overall TNM stage (8th edition)					
I	1415 (79.4)	96.7 (96.2–97.2)	1		
II	367 (20.6)	92.8 (91.4–94.2)	2.12	1.35–3.34	0.001
Extent of thyroidectomy					
Lobectomy	155 (8.7)	98.4 (97.3–99.5)	1		
Total thyroidectomy	1627 (91.3)	95.7 (95.2–96.2)	3.33	0.82–13.57	0.093
No. of LNs examined					
≤20	1458 (81.8)	96.8 (96.3–97.3)	1		
>20	324 (18.2)	91.8 (90.3–93.3)	3.01	1.93–4.71	<0.001
LN ratio					
≤0.25	1281 (71.9)	98.1 (97.7–98.5)	1		
<0.25	501 (28.1)	90.5 (89.2–91.8)	4.00	2.56–6.25	<0.001
Extranodal extension					
No	1,576 (88.4)	97.4 (97.0–97.8)	1		
Microscopic	206 (11.6)	84.7 (82.3–87.2)	5.53	3.55–8.62	<0.001
MACIS score					
<6	1539 (86.4)		1		
≥6	243 (13.6)		1.98	1.19–3.31	0.009

Abbreviations: CI, confidence interval; ETE, extrathyroidal extension; HR, hazard ratio; LN, cervical lymph node; MACIS, distant metastasis-age-invasion into surrounding area-completeness of resection-size of tumor; pTNM, pathological tumor-node-metastasis stage proposed by the American Joint Committee on Cancer; RAI, radioactive iodine.

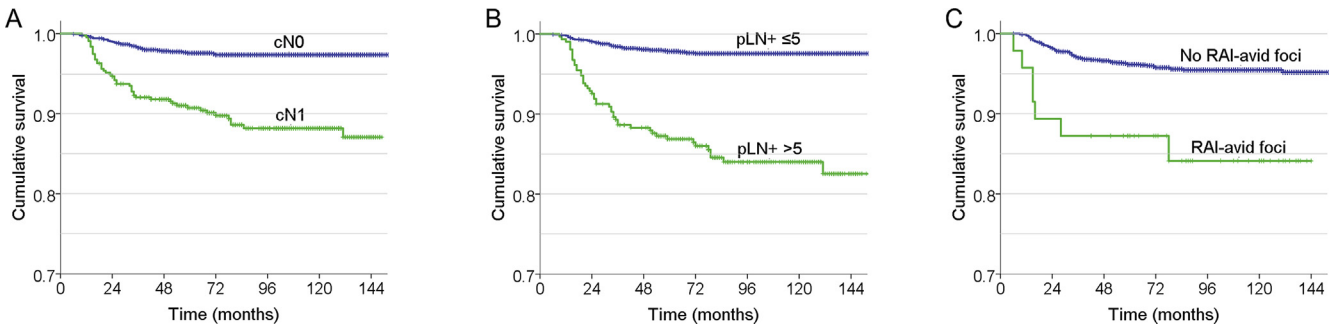

Fig. 1. Kaplan-Meier curves estimating recurrence-free survival according to the absence and presence of clinical nodal positivity (cN1, A), number of pathologically positive LN (pLN+) >5 (B), and RAI-avid metastatic foci (C) in PTC patients with ATA intermediate risk. Log-rank tests, $P < 0.005$.

Table 3
Multivariate analyses of factors related to recurrence-free survival.

Variable	Recurrence-free survival		
	HR	95% CI	*P*
ATA intermediate risk factors			
Clinical nodal positivity	2.15	1.28–3.63	0.004
No. of positive LNs >5	2.47	1.40–4.35	0.002
RAI-avid metastatic foci	2.56	1.18–5.59	0.018
Other clinicopathological factors			
LN ratio, >0.25	2.21	1.36–3.61	0.001
Microscopic extranodal extension	1.95	1.19–3.21	0.008
MACIS score, ≥6	1.82	1.08–3.05	0.024

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

rates were higher than the 95%, 74%, and 46% reported in the low-, intermediate-, and high-risk groups, respectively, in a retrospective cohort of 689 Pakistani PTC patients[27] and also slightly higher than the 7.4% reported previously for intermediate-risk disease recurrence.[17] A recent study from South Korea included 2425 patients comprising 633 (26.1%) with low risk, 1650 (68.0%) with intermediate risk, and 142 (5.9%) with high risk, as defined by the 2015 ATA risk stratification system.[15] Biochemical incomplete responses were observed in 6.2%, 15.2%, and 36.6% of patients in the low-, intermediate-, and high-risk groups, respectively, and structural incomplete responses were observed in 0.3%, 2.0%, and 7.7% of patients, respectively. The ATA risk stratification system was the independent factor of RFS, with a 4.6-fold higher recurrence risk in the intermediate-risk group compared to that in the low-risk group. The 2015 ATA guidelines much improved the practical performance of the 2009 guideline in terms of risk stratification for recurrence.[15] The differently reported recurrence rates in the ATA intermediate-risk group might result from differences in surgical extent, inclusion criteria, RAI therapy, etc.

Among the factors included in the 2015 ATA intermediate-risk category, cN1, pN1 >5 LNs, and RAI-avid metastatic foci were the independent factors predictive of posttreatment recurrence. The nodal factors related to clinical and pathological LN positivity and number appeared to significantly affect recurrence after thyroidectomy. A review paper proposed the prognostic significance of N1 in PTC based on positive LN size, number, and extranodal extension. Clinically, N positivity contributes to recurrence in 22% (range: 10–42%) of cN1 patients, a significantly higher rate than the 2% (range: 0–9%) in cN0 patients.[28] Thus, cN1 might be a more significant factor than microscopic LN metastasis in terms of recurrence prediction, with median recurrence risks of 4% (range: 3–8%) in pN1 patients with LNs <5 and a 19% (range: 7–21%) recurrence rate in those with LNs ≥5.[28] Furthermore, extranodal extension is associated with a median increased recurrence risk of 24% (range: 15–32%) as well as a worse cancer-specific survival in PTC patients.[28] The findings might be further supported by a previous study showing the prognostic risk factors of persistent or recurrent disease with number and extracapsular extension of N1 disease in PTC patients.[29] The prognostic significance of N1 in posttreatment recurrence has been also suggested in papillary thyroid microcarcinoma, with similar risk factors; e.g., positive LN number and extranodal extension.[30,31]

ETE is commonly described as microscopic, with minimal invasion (ATA intermediate risk), or macroscopic (ATA high risk), with invasion of the perithyroidal soft tissues or surrounding structures. The prognostic significance of microscopic ETE is controversial.[32] However, microscopic ETE might be associated with a lower RFS outcome compared that in patients without ETE.[33] Papillary thyroid microcarcinoma with microscopic ETE might be treated aggressively when co-presenting N1.[34] The extent of ETE in terms of microscopic (now classified as T1), macroscopic (T3), and macroscopic maximal (T4) might increase along with an increase in tumor size, showing different posttreatment outcomes and predicting nodal metastasis.[35,36] Most studies have shown that macroscopic ETE is associated with a higher rate of posttreatment disease recurrence compared to that for microscopic ETE.[32] Microscopic ETE appears to minimally affect posttreatment recurrence but might be considered a risk of recurrence when combined with multifocality and *BRAF*^{V600E} mutation.[12,37,38] RAI-avid metastatic foci outside the thyroid bed at initial posttreatment remnant ablation using whole-body RAI scans, as well as aggressive histology, have also been identified as a subset of patients with the

Table 4
Cox proportional hazard regression analyses of recurrence-free survival according to the positive number of ATA intermediate risk.

ATA intermediate risk	N (%)	5-y rate (95% CI)	Recurrence-free survival		
			HR	95% CI	*P*
Any single factor (1+)	960 (53.9)	98.6 (98.2–99.0)	1		
2+	494 (27.7)	96.3 (95.4–97.2)	1.72	0.88–3.32	0.111
3+	194 (10.9)	89.0 (86.7–91.3)	6.47	3.43–12.18	<0.001
≥4+	134 (7.5)	85.4 (82.3–88.5)	8.57	4.58–16.05	<0.001

HR, hazard ratio; CI, confidence interval.

increased risk of recurrence.[12]

The present study had the limitation that information on $BRAF^{V600E}$ mutation was not obtained in all study patients. Instead, microcarcinoma with ETE might be an alternative to the last risk factor added to the 2015 ATA intermediate-risk category. Nonetheless, the results of the present study might suggest more significant factors for recurrence, of those included in the 2015 ATA intermediate-risk category. In addition, Cox proportional hazard regression analyses showed a trend of 5-year decreasing RFS rates according to the positive number of ATA intermediate risk. Five-year RFS rate was 98.6% for patients with 1 risk factor and this decreased to 85.4% for patients with ≥4 risk factors. This might provide new information for risk stratification in the recent 2015 ATA guideline. Therefore, these results might help to guide clinicians in risk stratification and surgical planning involving lobectomy/total thyroidectomy and neck LN dissection.

In conclusion, the results of the present study suggest that cN1, >5 positive LNs, and the presence of RAI-avid metastatic foci might be independent factors associated with decreased RFS in patients with intermediate-risk PTC. Most PTC patients fall within the intermediate-risk group; however, this heterogeneous disease entity requires further evaluation. The results of the current study might help to define more significant factors of those in the 2015 ATA intermediate-risk group for posttreatment recurrence, and thus, potentially, impact clinical decision-making and risk stratification.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

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