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The definition of lymph node micrometastases in pathologic N1a papillary thyroid carcinoma should be revised

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ABSTRACT

Background: The aim of this study was to identify the risk factors for structural recurrence with a focus on lymph node–related factors and to determine the optimal cutoff size of lymph node micrometastases in patients with pathologic N1a classical papillary thyroid carcinoma.

Methods: We included patients who underwent total thyroidectomy with central compartment lymph node dissection for classic papillary thyroid carcinoma with pathologic N1a classification.

Results: A total of 398 patients were followed up for a median of 131 months. Structural recurrence occurred in 17.3% of patients (69/398). The multivariate analysis reported the following independent risk factors for structural recurrence: tumor size >1.95 cm, bilaterality, lymphatic and/or vascular invasion, a maximum diameter of the metastatic lymph node focus >3.5 mm, distribution of metastatic lymph node foci size >3.0 mm, and ≥4 metastatic lymph nodes.

Conclusion: The newly proposed cutoff of 3.5 mm for a definition of lymph node micrometastasis in pathologic N1a papillary thyroid carcinoma patients can reclassify the risk estimates of structural recurrence, thus modifying postoperative management plans and follow-up strategies.

Introduction

Pathologic lymph node (LN) metastasis in papillary thyroid carcinoma (PTC) has been identified as a risk factor for structural recurrence during the follow-up period after thyroidectomy. The current Tumor Node Metastasis Staging System of the American Joint Committee on Cancer/Union for International Cancer Control classifies pathologic LN metastases into pathologic N1a (pN1a) and N1b (pN1b), based solely on the location of the metastatic LNs[1]; however, this may not be the best tool for predicting the risk of recurrence after initial thyroid surgery.

Recently, the 2015 initial risk stratification system of the American Thyroid Association (ATA) added other LN-related risk factors, such as the maximal size of the metastatic LN foci (ie, 0.2 cm for the low- to intermediate-risk group and 3.0 cm for the intermediate- to high-risk group) and the number of metastatic LNs (ie, 5 for the low- to intermediate-risk group),[2] as risk factors for structural recurrence based on the results of previously published studies.[3–11] These studies, however, may have several limitations that affect the reliability of the results, including the relatively small numbers of enrolled patients, heterogeneity of the patient cohorts, and short follow-up periods. Furthermore, the LN-related risk factors for structural recurrence that were based on a cohort of pN1b PTC patients should not be applied uniformly to pN1a PTC patients because most of the LN-related risk factors in pN1b PTCs are likely to be more advanced and would have a greater prognostic effect on structural recurrence compared to the risk factors for pN1a PTCs. Therefore, a new set of LN-related risk factors for structural recurrence specific to pN1a patients must be identified. Furthermore, based on these data, the commonly used cutoff value of 0.2 cm for LN metastases should be validated and revisited for PTC because this cutoff value was derived from patients with breast cancer and other solid tumors.[3,8]

The aims of this study were to identify the risk factors for structural recurrence, with special consideration of LN-related factors,

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and to determine the optimal cutoff size of LN micrometastases in patients with pN1a classic PTC.

Materials and methods

Study population

We reviewed retrospectively all patients who underwent a total thyroidectomy with central compartment node dissection (CCND) followed by radioactive iodine (RAI) ablation of any remnant thyroidal tissue for classic PTC with pN1a at the Asan Medical Center, Seoul, Korea, between 2000 and 2005. The pN1a classification was confirmed on the final pathology report after thyroidectomy for all patients. To ensure a more homogenous study population, the following patients were excluded from this study: those who had a distant metastasis at the time of initial diagnosis or within 12 months after the initial operation; those who were classified as T4a; those who did not receive RAI remnant ablation; those who had a follow-up period of less than 12 months; and those who had insufficient medical records. The clinicopathologic data of the patients were gathered from medical records with special consideration given to the following LN-related factors: the maximum diameter of the foci within the metastatic LN, which was measured from the largest metastatic focus and not the size of the LN itself; the number of metastatic LNs; the number of retrieved LNs; the metastatic LN ratio, which was defined as the number of metastatic LNs divided by the number of retrieved LNs; and any extranodal extension (ENE).

Data were obtained from a prospectively maintained endocrine surgery database at the Asan Medical Center. The study protocol was approved by our Institutional Review Board, and the requirement for informed consent from each patient was waived because of the noninterventional nature of the study.

Preoperative diagnosis and staging workup

Ultrasonography-guided fine needle aspiration cytology or core needle biopsy were used to perform the preoperative diagnosis. For the preoperative diagnosis of PTC in all cases, preoperative staging workup using both high-resolution neck ultrasonography and computed tomography (CT) was performed to evaluate the tumor characteristics and cervical lymph node status, including the presence or absence of lateral LN metastases.

Operative strategy and follow-up protocols

All patients underwent a total thyroidectomy with CCND and received subsequent RAI remnant ablation. At our institution, CCND was performed routinely for patients with PTC who required a total thyroidectomy; at a minimum, we performed unilateral prophylactic CCND even in the absence of suspicious LNs on preoperative imaging studies or during operation. Bilateral CCND was performed on patients with suspicious LNs, those with LN enlargement in the contralateral central compartment, or those with bilateral cancer. All operative procedures were performed by 1 experienced endocrine surgeon (S.J.H.). A formal compartment-based nodal dissection was performed over the selective “berry-picking” technique.

All patients received subsequent RAI remnant ablation at 2 to 3 months postoperatively. The RAI dose was set according to the protocol established by the Endocrinology Division of the Asan Medical Center. After RAI remnant ablation, all patients followed-up regularly every 6–12 months to ensure suppression of thyroid-stimulating hormone (TSH) without thyrotoxicosis, which was assessed by serial measurements of serum thyroglobulin (Tg)/anti-Tg antibody and neck ultrasonography. Any patient suspected of having locoregional recurrence underwent ultrasonography-guided fine needle aspiration cytology. Distant metastasis was diagnosed using whole-body iodine scintigraphy, chest CT, or 18F-fluorodeoxyglucose positron emission tomography/CT and was confirmed by serial imaging or biopsy.

Structural recurrence was defined as the appearance of cytologically or histopathologically proven malignant tissue, or the appearance of highly suspicious structural lesions on serial cross-sectional or functional imaging studies after a 1-year minimum period of no evidence of disease (NED) after the initial treatment. Unlike extracervical structural lesions (ie, distant metastasis), locoregional recurrence was diagnosed as recurrence only after confirmation by tissue biopsy. Biochemical recurrence, which was characterized by an increased serum Tg level but without clinical evidence of structural disease was not classified as true recurrence.

Statistical analyses

Categorical variables were presented as numbers and percentages, and continuous variables were presented as the mean ± standard deviation or the median (range) depending on the distribution of the data. The risk factors for structural recurrence were evaluated using univariate/multivariate Cox proportional hazard models. A multivariate analysis was performed to assess the well-known risk factors reported by previous studies and to determine the statistically significant risk factors from the univariate analysis of this study. To improve the clinical utility of this study, some of the continuous variables that were proven to be independent risk factors by the multivariate analysis were converted into categorical variables with cutoff values and areas under the curve (AUCs) calculated by the Rmax stat package based on log rank tests. Curves of recurrence-free survival (RFS) were constructed using the Kaplan-Meier method, and log rank tests were used to evaluate the differences in RFS among the groups. All P values were 2-sided, and a $P < 0.05$ was considered statistically significant. R version 3.3.1 and the R libraries car and Cairo were used to analyze the data (R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinicopathologic characteristics

From 2000 to 2005, 601 patients underwent a total thyroidectomy with CCND for classic PTC. After excluding patients based on the criteria mentioned previously, 398 patients were included in this study; their clinicopathologic characteristics are summarized in Table 1.

The median follow-up duration was 131 months (range, 13–197 months). Structural recurrence occurred in 17.3% (69/398) of the patients, including locoregional recurrence in 65 patients and distant metastasis in 5. A total of 3 patients developed both locoregional recurrence and distant metastasis. The site of locoregional recurrence included the central LNs in 1 patient and the previously undissected lateral LNs in 64 patients. Distant metastases were found in the lungs (3/5), bone (1/5), and multiple tissues (1/5). Four patients (1.1%) died of advanced PTC. The median interval between initial treatment and structural recurrence was 45 months (range, 13–161 months).

Analysis of the risk factors for structural recurrence

The univariate analysis showed that primary tumor size, bilaterality, any lymphatic and/or vascular invasion, ENE, maximum diameter of the metastatic foci of LNs, distribution of the size of the metastatic LN foci, number of metastatic LNs, and

Table 1
Baseline clinicopathologic characteristics of 398 study patients with pN1a papillary thyroid carcinoma.

Parameters		Total no. of patients = 398
Age (years, median [range])		45.5 (9.6–73.7)
Sex, *n* (%)	Female	347 (87.2)
	Male	51 (12.8)
Tumor size (cm, median [range])		1.55 (0.20–8.00)
Extrathyroid extension, *n* (%)	No	139 (32.9)
	Yes	267 (67.1)
Multifocality, *n* (%)	No	236 (59.3)
	Yes	162 (40.7)
Bilaterality, *n* (%)	No	290 (72.9)
	Yes	108 (27.1)
Lympho-vascular invasion*	No	370 (93.0)
	Yes	28 (7.0)
Extranodal extension	No	318 (79.9)
	Yes	80 (20.1)
Metastatic LN focus size (mm)†		3.00 (1.00–20.00)
Distribution of metastatic LN focus size (mm), *n* (%)	1.0–1.9	110 (27.6)
	2.0–2.9	79 (19.9)
	3.0–4.9	89 (22.4)
	5.0–9.9	90 (22.6)
	10.0–19.9	28 (7.0)
	≥20.0	2
Total number of retrieved LNs†		9.0 (1.0–30.0)
Total number of metastatic LNs†		3.0 (1.0–17.0)
Metastatic LN ratio†		0.33 (0.04–1.00)
Structural recurrence, *n* (%)	No	329 (82.7)
	Yes	69 (17.3)

SD, standard deviation.
* Combined numbers for either lymphatic or vascular invasion.
† Values are presented as the median (range).

metastatic LN ratio were potential risk factors for structural recurrence (Table 2). The multivariate analysis reported the following independent risk factors for structural recurrence: tumor size >1.95 cm (AUC = 0.691), bilaterality, lymphatic or vascular invasion, maximum metastatic LN foci diameter of 3.5 mm (AUC = 0.713), distribution of metastatic LN foci size (>3.0 mm), and ≥4 metastatic LNs (AUC = 0.693; Tables 2 and 3). These variables should be considered risk factors of structural recurrence in lateral LNs, which comprised most of the recurrence sites in this study.

Interestingly, the mean metastatic size of the LN foci in the group with NED was very close to the cutoff size of 3.5 mm, and this factor was presumed to be associated with the 15 patients with metastatic LN foci ≥10 mm who were included in the NED group.

Comparison of RFS based on each independent risk factor for structural recurrence

The 5- and 10-year RFS rates were 93.6% and 85.8%, respectively. The RFS rates were significantly less in patients who demonstrated each of the independent risk factors for structural recurrence than in those of their counterparts (Fig. 1).

Discussion

This study revealed that various factors affect the risk of structural recurrence during the follow-up period of patients with pN1a classic PTC. In particular, patients with a primary tumor size >1.95 cm, bilateral tumors, or lymphatic or vascular invasion were more likely to develop structural recurrence. The LN-related factors that were statistically significant were a maximum LN metastatic foci of >3.5 mm and ≥4 metastatic LNs. Furthermore, most patients developed structural recurrence in previously undissected lateral LNs.

In addition to the location of the metastatic LNs, several previously published studies have demonstrated that the metastatic LN ratio,[9,10] the maximum size of the metastatic foci,[3,4,7,8] the number of metastatic LNs,[5,6,8,11] and ENE[6,8] had prognostic impacts on the development of structural recurrence. Moreover, our previous study found that a maximum diameter of LN metastatic foci >2.0 cm, a central metastatic LN ratio >0.42, and ENE were independent risk factors for structural recurrence in patients with pN1b classic PTC.[12] Likewise, this present study revealed that LN-related factors, including the maximum size of the LN metastatic foci and the number of metastatic LNs, significantly influenced structural recurrence in patients with pN1a classic PTC. Based on these collaborative results in the literature, the initial risk stratification system of the ATA and the guidelines of the National Comprehensive Cancer Network (NCCN) have been revised, with the addition of the number and maximum size of the LN metastatic foci as 2 factors for classifying those risk groups.[2,13]

The present study focused on determining the cutoff value for the maximum size of the LN metastatic foci that could be used to divide the ATA into low- and intermediate-risk groups. A large size (>3.0 cm) of LN metastatic foci was a strong risk factor for structural recurrence in previous cohorts of patients with PTC, but the traditional cutoff of <0.2 cm for LN micrometastasis has not yet been confirmed for PTC.[3,8] Although this classification is in line with the commonly accepted pathologic definition,[14,15] this definition was derived from breast cancer and other solid tumors—not PTCs. Moreover, most of the previously published studies might have been designed inappropriately to define the cutoff of LN micrometastases. Because these studies included patients with both pN1a and pN1b PTC, the LN-related factors associated with the pN1b classification were more intense and had stronger prognostic effects than those associated with the pN1a classification.

Our present study included only patients with pN1a PTC to better evaluate their LN-related risk factors for structural recurrence and to determine an appropriate cutoff of LN micrometastases. Indeed, we found that *P* value for the maximum diameter of LN metastatic focus of >3.5mm is <0.001, was an independent risk factor with marginal statistical significance for structural recurrence in patients with pN1a PTC (AUC = 0.713). This result was consistent with the recently revised guidelines of the NCCN for thyroid carcinoma,[13] which suggest that large volume pN1 metastases (ie, >5 nodes with micrometastases and >0.5 cm in the largest dimension) adversely affect prognosis, whereas LN micrometastases (with a maximum dimension of ≤0.5 cm) were associated with a low risk of recurrence. Considering the indolent nature and excellent prognosis of PTCs compared to breast cancer and other solid tumors, it makes sense to establish the definition of LN micrometastases in PTCs based on data collected from a large cohort of patients with pN1a PTC who were followed for a greater period. If the definition of LN micrometastases can be modified based on our results, the patients who have a maximum diameter of LN metastatic focus in the range of 2.0–3.5 mm would be reclassified as having a low risk for structural recurrence. Therefore, they require less intensive follow-up examinations at longer intervals and less intensive TSH suppression therapy. Conversely, the patients with risk factors for structural recurrence should follow up more frequently (every 6 months) for 4 years after their initial treatments, considering the hazard ratio of each risk factor, with serologic markers, including Tg, anti-Tg Ab, TSH levels, and imaging studies, including neck ultrasonography and neck CT, with special consideration of lateral LN metastasis. Furthermore, the risk factors for structural recurrence in the present study can be applied consistently even to patients undergoing less-extended initial treatment because these factors had substantial effects on postsurgical outcomes, although the patients included in the present study had received the maximal initial treatment.

Notably, the patients enrolled in the present study had a high rate of structural recurrence, most of which occurred in previously

Table 2
Univariate and multivariate analysis of risk factors for structural recurrence in patients with pN1a PTC.

Parameters	NED (329 patients)	Recur (69 patients)	Univariate		Multivariate	
			Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age (years, mean ± SD)	45.49 ± 12.00	41.8 ± 13.8	0.98 (0.96–1.00)	.061	0.99 (0.98–1.01)	.517
Sex, *n* (%)				.510		.749
Female	288 (87.5)	59 (86)	Ref.		Ref.	
Male	41 (12.5)	10 (145)	1.25 (0.64–2.45)		0.89 (0.45–1.78)	
Tumor size (cm, mean ± SD)	1.7 ± 1.0	2.4 ± 1.3	1.44 (1.25–1.66)	<.001	1.25 (1.06–1.48)	.009
Extrathyroid extension				.170		.309
No	110 (33.4)	21 (30)	Ref.		Ref.	
Yes	219 (66.6)	48 (70)	1.39 (0.87–2.25)		1.36 (0.75–2.46)	
Multifocality, *n* (%)				.096		.237
No	202 (61.4)	34 (49)	Ref.		Ref.	
Yes	127 (38.6)	35 (51)	1.49 (0.93–2.39)		1.27 (0.63–2.53)	
Bilaterality, *n* (%)						
No	249 (75.7)	41 (59)	Ref.		Ref.	
Yes	80 (24.3)	28 (41)	1.99 (1.23–3.23)	.005	2.09 (1.04–4.18)	.038
Lympho-vascular invasion†				<.001		.005
No	314 (95.4)	56 (81)	Ref.		Ref.	
Yes	15 (4.6)	13 (18)	3.56 (1.94–6.51)		2.45 (1.32–4.54)	
Extranodal extension				<.001		.113
No	276 (83.9)	42 (61)	Ref.		Ref.	
Yes	53 (16.1)	27 (39)	3.07 (1.89–4.98)		1.56 (0.90–1.01)	
Metastatic LN focus size (mm)*	3.4 ± 3.1	6.0 ± 4.3	1.15 (1.10–1.21)	<.001	1.11 (1.05–1.18)	.001
Distribution of metastatic LN focus size (mm), *n* (%)						
1.0–1.9	103 (31.3)	7 (10)	Ref.		Ref.	
2.0–2.9	72 (21.9)	7 (10)	1.49 (0.52–4.24)	.459	1.39 (0.48–3.97)	.543
3.0–4.9	71 (21.6)	18 (26)	3.40 (1.42–8.14)	.006	2.54 (1.04–6.22)	.041
5.0–9.9	68 (20.7)	22 (32)	4.35 (1.86–10.19)	.001	3.67 (1.53–8.78)	.004
10.0–19.9	13 (4.0)	15 (22)	13.04 (5.31–32.03)	<.001	8.33 (3.25–21.35)	<.001
≥ 20.0	2	0	NA	NA	NA	NA
Total number of retrieved LNs*	10.24 ± 5.31	10.20 ± 5.09	0.99 (0.95–1.04)	.780	1.29 (0.64–3.24)	.388
Total number of metastatic LNs*	3.35 ± 2.69	5.74 ± 4.10	1.17 (1.11–1.24)	<.001	1.32 (1.07–1.61)	.008
Metastatic LN ratio*	0.37 ± 0.26	0.56 ± 0.26	3.87 (1.42–7.81)	<.001	1.14 (0.96–2.30)	.172

CI, confidence interval; NA, not applicable; Ref., reference; SD, standard deviation.
* These values are presented as the mean ± standard deviation to compare between the NED group and the recur group.
† Combined numbers for either lymphatic or vascular invasion.

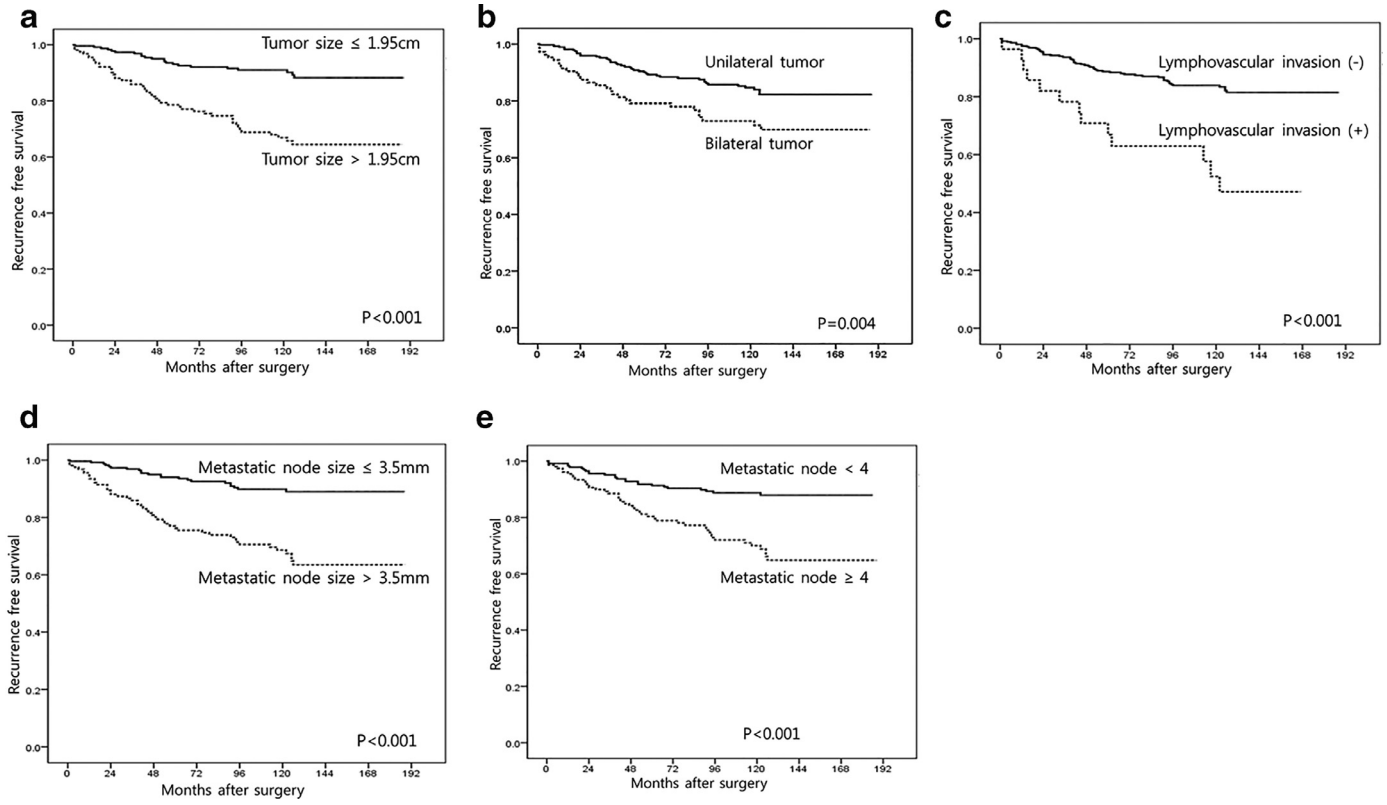

Fig. 1. Comparison of the rates of recurrence-free survival with the presence of each independent risk factor: (A) tumor size, (B) bilaterality, (C) lymphatic and/or vascular invasion, (D) size of the metastatic LN foci, and (E) number of metastatic lymph nodes.

Table 3
Independent risk factors for structural recurrence and their hazard ratios in patients with pN1a PTC

	Hazard ratio (95% CI)	*P*
Primary tumor size (>1.95 cm)*	3.75 (2.26–6.22)	<.001
Bilaterality	1.99 (1.23–3.23)	.005
Lymphovascular invasion (present)†	3.56 (1.94–6.51)	<.001
Metastatic LN focus size (>3.5 mm)*	3.76 (2.27–6.24)	<.001
Total number of metastatic LNs (≥4)	3.01 (1.82–4.92)	<.001

CI, confidence interval.
* These cutoff values were calculated by Maxstat of R based on log rank test statistics.
† Combined numbers for either lymphatic or vascular invasion.

undissected lateral LNs. This high rate of recurrence was presumed to be associated with our inclusion criteria. All of our patients received RAI remnant ablation, which meant that these patients were classified as having an intermediate or high risk for structural recurrence based on their histopathologic findings. The recurrence rate in the initial patient cohort of patients with both pN0 and pN1a disease who underwent total thyroidectomy with CCND regardless of RAI remnant ablation was 14.4% (87/601). In addition, in our previously published study on patients with pNX and pN0 PTC who underwent the same operative treatment, the recurrence rate was only 2.2%.[16] Furthermore, given the vast majority of patients with structural recurrence that occurred in previously undissected lateral LNs, short-term intensive follow-up imaging studies to identify the presence of newly developed lateral LN metastases must be considered in patients with pN1a PTC who display risk factors for structural recurrence. Nevertheless, the rate of structural recurrence (17.0%) in the present study was greater than what has been reported in previously published studies (5-year recurrence rate, 3.1%–8.9%; 10-year recurrence rate, 7.4%–13.0%) in the same patient cohort.[17–19] Although the exact reason for this greater rate of recurrence could not be clearly explained, the greater frequency of $BRAF^{V600E}$ mutations in PTC (52.0%–83.0%) in the Korean population than that reported (30.0%–49.0%) in other countries was presumed to be a possible cause.[20]

This clinicopathologic investigation of 398 patients with pN1a classic PTC had a relatively larger scale and greater follow-up duration than previous studies; however, it contains several limitations inherent to retrospective studies. To overcome these limitations, the present study was limited to a very specific, homogenous cohort of patients who all underwent the same extent of thyroid surgery for classic PTC by 1 experienced surgeon at a single institution. Furthermore, based on the preference of prophylactic LN dissection for PTCs at our institution, all the LN-related factors could be evaluated in detail. Moreover, to minimize selection bias and to clearly evaluate the effect of LN-related factors on structural recurrence, we excluded patients who had distant metastasis at the time of initial diagnosis or within 12 months after the initial operation, those who had a follow-up period of less than 12 months, and those who were diagnosed with variants of PTC. The lack of data on the extent of CCND (unilateral versus bilateral), however, which might have affected the outcome, might be another limitation of the present study.

This study suggested the possibility of revising the definition of LN micrometastases in patients with pN1a classic PTC. Reclassifying a patient's risk for structural recurrence based on this revised definition of LN micrometastases may modify the postoperative management plan, including RAI remnant ablation or the degree of TSH suppression, and it may affect the intensity and interval of follow-up visits during the postoperative period in patients with pN1a PTC.

Conflicts of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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