Original Article

Risk factors associated with high-risk nodal disease in patients considered for active surveillance of papillary thyroid microcarcinoma without extrathyroidal extension

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Background: Active surveillance (AS) has become an alternative treatment approach for papillary thyroid microcarcinoma (PTMC). The purpose of this study is to uncover the clinicopathological factors associated with high-risk nodal disease in order to select proper candidates for AS of PTMC.

Methods: We retrospectively reviewed 5,329 patients with PTMC without extrathyroidal extension (ETE) who underwent thyroidectomy with central compartment neck dissection (CCND) between 2007 and 2021 at Seoul St. Mary's Hospital. Patients with more than five metastatic lymph nodes (MLNs) (higher-risk N1 disease) and/or lateral neck node metastases (N1b disease) were defined as having high-risk nodal disease. The clinicopathological factors associated with high-risk nodal disease were analyzed.

Results: A total of 415 (7.8%) patients had higher-risk N1 disease. These patients were younger on average, included a higher proportion of males, and had a larger tumor size and more frequent capsular invasion and multifocality compared with other patients. For the tumor size, a cutoff value of 0.65 cm was the best predictor of nodal risk groups. In a multivariate analysis, the independent risk factors associated with higher-risk N1 disease were younger age, male sex, tumor size >0.65 cm, and the presence of capsular invasion and/or multifocality. A total of 246 (4.6%) patients had N1b disease at initial diagnosis. In a multivariate analysis, the independent risk factors associated with N1b disease were younger age, male sex, tumor size >0.65 cm, and the presence of capsular invasion and/or multifocality.

Conclusions: Young age, male sex, tumor size >0.65 cm, and presence of capsular invasion and/or multifocality can be considered risk factors for high-risk nodal disease in PTMC. Therefore, cautious observation is necessary for AS of patients with these characteristics.

Keywords: Papillary thyroid carcinoma (PTC); thyroid cancer; active surveillance (AS); higher-risk N1; lymph node metastasis

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Introduction

The number of patients diagnosed with papillary thyroid microcarcinoma (PTMC), defined as a papillary thyroid carcinoma (PTC) tumor ≤1 cm in size, has increased with the prevalence of neck ultrasonography (1,2). After surgery, the disease-specific mortality rate of PTMC is reported to be <1% (2). Because of the indolent nature of PTMC, Ito *et al.* recommended prospective clinical studies to determine the suitability of active surveillance (AS) for patients with PTMC (3,4). AS has been introduced as a major treatment approach for PTMC and is currently being applied worldwide.

Factors to distinguish which patients have stable disease and which patients will experience disease progression during AS have not yet been clearly identified (1,5). Disease progression can only be detected after tumor size enlargement or novel appearance of lymph node metastasis on ultrasonography during follow-up (3,6). There are still no reliable molecular markers that can predict tumor progression during AS (1,5). Several clinical factors, including young age and pregnancy, have been reported as aggravating factors that promote tumor enlargement during AS of PTMC (3,7).

Progression through nodal metastasis is difficult to predict because of the low sensitivity of metastasis detection in central lymph nodes, despite the high incidence of occult lymph node metastasis in the central compartment area (8-13). Furthermore, nodal characteristics associated with risk of recurrence, including size of metastatic foci, number of metastatic nodes, and extra-nodal extension, are difficult to determine by preoperative ultrasonography (8,9,14-17). In addition, if node metastasis occurs in the lateral neck during AS, the extent of surgery and the need for adjuvant treatment will be different than in cases without metastasis, so the prediction of lymphatic metastasis is important (1,18). The purpose of this study is to determine the risk factors associated with high-risk nodal disease in PTMC in order to identify proper and safe candidates for AS before surgery. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-256/rc).

Highlight box

Key findings

- We analyzed factors associated with high-risk nodal disease in papillary thyroid microcarcinoma (PTMC).

What is known and what is new?

- The presence of more than five metastatic lymph nodes is known to show relatively poor prognosis and is classified as 'higher-risk N1 disease'. However, occult lymph node metastasis is common in PTMC. Active surveillance (AS) has been suggested as an alternative to immediate surgery, therefore, we tried to find out factors that can predict lymph node metastasis without surgery.
- Among a total of 5,329 patients with PTMC, 7.8% (n=415) had higher-risk N1 disease and 4.6% (n=246) had N1b disease. Young age, male sex, tumor size >0.65 cm, capsular invasion, and multifocality are risk factors related to high-risk nodal disease.

What is the implication, and what should change now?

- A judicious follow-up approach is necessary for patients with PTMC during AS, considering the above characteristics.

Methods

Patients

We used our Clinical Data Warehouse system to retrospectively review the medical records of patients with PTMC who underwent thyroidectomy with central compartment neck dissection (CCND) from 2007 through 2021 at Seoul St. Mary's Hospital, College of Medicine, the Catholic University of Korea. Patients that underwent lateral neck dissection as initial treatment for lateral neck metastases were also included. Patients who had extrathyroidal extension (ETE) on final pathologic report were excluded. Patients with reoperation due to recurrence were excluded. In total, 5,329 patients were enrolled for analysis. The treatment policy of our institution for PTMC without lateral neck metastasis has been changed by guidelines. Before 2009, total thyroidectomy with prophylactic CCND for all differentiated thyroid carcinomas was the standard treatment in our institution (19,20). From 2009 onward, unilateral thyroid lobectomy with prophylactic CCND was performed for PTMC found to be limited to a unilateral lobe without ETE on preoperative evaluation (1,21). From 2014 onward, thyroid isthmusectomy with prophylactic CCND was performed for patients with a single tumor located on the thyroid isthmus (22). Total thyroidectomy with bilateral CCND and therapeutic lateral neck dissection has been the standard procedure for patients with lateral neck node metastasis.

Nodal status evaluation

The patients were categorized as having high-risk or low-

Table 1 The clinicopathological characteristics of the total PTMC cohort

Variables	Value (n=5,329)
Age (years)	46.4±11.8 [13–82]
Age (<55:≥55 years)	3,978 (74.6):1,351 (25.4)
Sex (female:male)	4,251 (79.8):1,078 (20.2)
Tumor size (cm)	0.62±0.20 [0.08–1.00]
Multifocality	
No	3,440 (64.6)
Yes	1,889 (35.4)
Capsular invasion	
No	2,992 (56.1)
Yes	2,337 (43.9)
Nodal status	
Metastasis	
No	2,948 (55.3)
Yes	2,381 (44.7)
Number of MLNs	1.59±3.10 [0–32]
Higher-risk N1	415 (7.8)
N1b	246 (4.6)
Thyroidectomy	
Total thyroidectomy	2,550 (47.9)
Unilateral lobectomy	2,632 (49.4)
Isthmusectomy	147 (2.8)

Data are presented as mean ± SD [min–max] or n (%). Higher-risk N1: patients with more than five MLNs. PTMC, papillary thyroid microcarcinoma; MLN, metastatic lymph node; SD, standard deviation.

risk nodal disease according to their nodal status. In terms of the volume of metastatic disease, patients with more than five metastatic lymph nodes (MLNs) were classified as having higher-risk N1 disease, because they are known to have an elevated recurrence rate, whereas patients with five or fewer MLNs were classified as having lower-risk N disease (1,17). In terms of the anatomical site of metastasis, patients with lymph node metastases located on the lateral neck (N1b disease) were classified separately regardless of the number of lymph node metastases, because the presence of lateral neck node metastases at initial diagnosis requires total thyroidectomy with therapeutic selective neck dissection followed by radioactive iodine (RAI) therapy regardless of tumor size or American Thyroid Association (ATA) risk stratification (1,18). Thus, patients with higher-risk N1 disease or N1b disease were defined as having high-risk nodal disease in this study.

Statistical analysis

Clinicopathologic characteristics were analyzed to evaluate the variables related to lymph node metastasis in PTMC. Continuous, quantitative data are expressed as the mean ± standard deviation (SD). Categorical, qualitative data are expressed as frequencies and percentages.

The chi-squared test or Mann-Whitney *U* test was used to compare categorical variables. Student's *t*-test was used to analyze the means of continuous variables. Univariate and multivariate analyses were performed using logistic regression to identify factors associated with lymph node metastasis. All statistical analyses were performed using SPSS version 24.0 (released 2016; IBM SPSS Statistics for Windows, version 24.0; IBM Corp., Armonk, NY, USA).

Ethical statement

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, the Catholic University of Korea (No. KC22WISI0219) and individual consent for this retrospective analysis was waived.

Results

The clinicopathological characteristics of the total PTMC cohort (Table 1)

The total cohort of 5,329 patients had a mean age at diagnosis of 46.4±11.8 (range, 13–82) years and included 1,078 males (20.2%) and 4,251 females (79.8%) (*Table 1*). The mean tumor size was 0.62±0.20 (range, 0.08–1.00) cm. Multifocal cancers were present in 1,889 (35.4%) patients, and capsular invasion was found in 2,337 (43.9%) patients. Lymph node metastasis was found in 2,381 (44.7%) patients. The mean number of MLNs was 1.59±3.10 (range, 0–32). Among the patients with lymph node metastasis, higher-risk N1 disease and N1b disease were found in 415 (7.8%) patients and 246 (4.6%) patients, respectively, at initial diagnosis. In terms of the extent of thyroidectomy, 2,550 (47.9%) patients underwent

Table 2 The clinicopathologic characteristics between higher-risk N1 and lower-risk N disease

Variables	Higher-risk N1 (n=415)	Lower-risk N (n=4,914)	P value
Age (years)	42.4±12.9 [17–80]	46.7±11.7 [13–82]	<0.001
Age (<55:≥55 years)	338 (81.4):77 (18.6)	3,640 (74.1):1,274 (25.9)	0.001
Age			<0.001
10s and 20s	56 (13.5)	334 (6.8)	
30s and 40s	242 (58.3)	2,520 (51.3)	
≥50s	117 (28.2)	2,060 (41.9)	
Sex (female:male)	243 (58.6):172 (41.4)	4,008 (81.6):906 (18.4)	<0.001
Tumor size (cm)	0.72±0.20 [0.1–1.0]	0.61±0.20 [0.08–1.00]	<0.001
Tumor size			<0.001
≤0.65 cm	151 (36.4)	2,840 (57.8)	
>0.65 and ≤1 cm	264 (63.6)	2,074 (42.2)	
Multifocality			<0.001
No	183 (44.1)	3,257 (66.3)	
Yes	232 (55.9)	1,657 (33.7)	
Capsular invasion			<0.001
No	132 (31.8)	2,860 (58.2)	
Yes	283 (68.2)	2,054 (41.8)	
Nodal status			
Metastasis			<0.001
No	0 (0.0)	2,948 (60.0)	
Yes	415 (100.0)	1,966 (40.0)	
Number of MLNs	10.1±4.8 [6–32]	0.88±1.30 [0–5]	<0.001
N1b	154 (37.1)	92 (1.9)	<0.001
Thyroidectomy			<0.001
Total thyroidectomy	315 (75.9)	2,235 (45.5)	
Unilateral lobectomy	94 (22.7)	2,538 (51.6)	
Isthmusectomy	6 (1.4)	141 (2.9)	

Data are presented as mean ± SD [min–max] or n (%). Higher-risk N1 group: patients with more than five MLNs; lower-risk N group: patients with no or less than equal to five MLNs. MLN, metastatic lymph node.

total thyroidectomy, 2,632 (49.4%) patients underwent unilateral lobectomy, and 147 (2.8%) patients underwent isthmusectomy.

The clinicopathological characteristics of higher-risk N1 disease (Table 2)

A total of 415 (7.8%) patients were classified as having higher-risk N1 disease. Compared with the other patients, these patients were younger (mean age, 42.4 *vs.* 46.7 years, P<0.001) and had a higher proportion of males (41.4% *vs.* 18.4%, P<0.001). In terms of tumor characteristics, the patients with higher-risk N1 disease had larger tumor sizes (0.72 *vs.* 0.61 cm, P<0.001) and higher frequencies of multifocality (55.9% *vs.* 33.7%, P<0.001) and capsular invasion (68.2% *vs.* 41.8%, P<0.001) compared with the

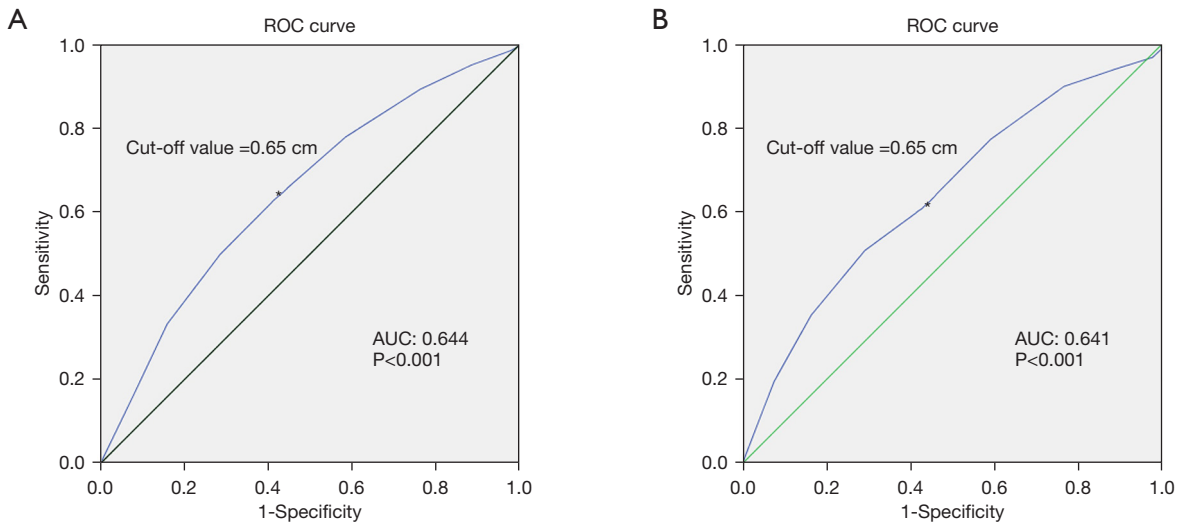

Figure 1 ROC curves for predicting higher-risk N1 disease (A) and N1b disease (B). *, cut-off value. Higher-risk N1: patients with more than five MLNs. ROC, receiver operating characteristic; AUC, area under the curve; MLN, metastatic lymph node.

other patients (*Table 2*). Receiver operating characteristic (ROC) curve analysis was performed to establish the optimal cutoff of tumor size to attribute an elevated risk of nodal involvement to the patients with higher-risk N1 disease (*Figure 1A*). The optimal cutoff value was 0.65 cm with an area under the curve (AUC) of 0.644. The sensitivity and specificity for prediction of nodal involvement based on this cutoff value were 0.636 and 0.580, respectively. The value of 0.65 cm for tumor size was applied as the cutoff level for subsequent analysis. Among the patients with five or fewer MLNs, 2,948 (60.0%) patients showed no metastasis, and 1,966 (40.0%) patients showed at least one MLN. The mean number of MLNs was 10.1±4.8 (range, 6–32) among the patients with higher-risk N1 disease and 0.88±1.30 (range, 0–5) among the other patients (P<0.001). One hundred and fifty-four (37.1%) of the patients with higher-risk N1 disease were classified as having N1b disease, and another 92 (1.9%) patients with five or fewer MLNs were classified as having N1b disease (P<0.001). Total thyroidectomy was more frequent among the patients with higher-risk N1 disease than among the other patients (75.9% *vs.* 45.5%, P<0.001).

The clinicopathological factors associated with higher-risk N1 disease (Table 3)

Logistic regression analysis was performed to analyze the clinicopathological characteristics associated with higher-risk N1 disease (*Table 3*). On univariate analysis, younger age was associated with higher-risk N1 disease. Compared with patients 50 years of age or older, patients in their 30s and 40s {hazard ratio (HR) [95% confidence interval (CI)], 1.691 (1.346–2.124), P<0.001} or in their 10s and 20s [HR (95% CI), 2.952 (2.104–4.143), P<0.001] had a higher risk of N1 disease. In addition, male sex [HR (95% CI), 3.131 (2.543–3.856), P<0.001], tumor size >0.65 cm [HR (95% CI), 2.394 (1.945–2.947), P<0.001], presence of capsular invasion [HR (95% CI), 2.985 (2.410–3.698), P<0.001], and presence of multifocality [HR (95% CI), 2.492 (2.035–3.052), P<0.001] were factors related to higher-risk N1 disease. In the multivariate analysis, younger age was an independent risk factor associated with higher-risk N1 disease [30s and 40s: HR (95% CI), 1.827 (1.440–2.317), P<0.001; 10s and 20s: HR (95% CI), 3.757 (2.613–5.389), P<0.001]. Male sex [HR (95% CI), 3.236 (2.607–4.017), P<0.001], tumor size >0.65 cm [HR (95% CI), 1.816 (1.460–2.260), P<0.001], presence of capsular invasion [HR (95% CI), 2.523 (2.014–3.160), P<0.001], and presence of multifocality [HR (95% CI), 2.342 (1.897–2.891), P<0.001] remained as independent risk factors to increase the nodal risk to a higher level.

The clinicopathological characteristics of N1b disease (Table 4)

A total of 246 (4.6%) patients were confirmed to have N1b disease at initial diagnosis. Compared with the other patients, the patients with N1b disease had a similar mean

Table 3 The clinicopathological factors associated with higher-risk N1 disease

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age				
≥50s		Ref.		Ref.
30s and 40s	1.691 (1.346–2.124)	<0.001	1.827 (1.440–2.317)	<0.001
10s and 20s	2.952 (2.104–4.143)	<0.001	3.757 (2.613–5.389)	<0.001
Sex				
Female		Ref.		Ref.
Male	3.131 (2.543–3.856)	<0.001	3.236 (2.607–4.017)	<0.001
Tumor size				
≤0.65 cm		Ref.		Ref.
>0.65 and ≤1 cm	2.394 (1.945–2.947)	<0.001	1.816 (1.460–2.260)	<0.001
Capsular invasion				
No		Ref.		Ref.
Yes	2.985 (2.410–3.698)	<0.001	2.523 (2.014–3.160)	<0.001
Multifocality				
No		Ref.		Ref.
Yes	2.492 (2.035–3.052)	<0.001	2.342 (1.897–2.891)	<0.001

HR, hazard ratio; CI, confidence interval; ref., reference.

age but a larger average tumor size (0.72 *vs.* 0.62 cm, P<0.001), higher proportions of males (30.5% *vs.* 19.7%, P<0.001), and patients younger than 40 years of age (39.4% *vs.* 30.9%, P=0.005). The optimal cutoff of tumor size for the N1b analysis was 0.65 cm with an AUC of 0.641. The sensitivity and specificity of N1b disease prediction with this cutoff value were 0.610 and 0.570, respectively (*Figure 1B*). The patients with N1b disease had higher frequencies of multifocality and capsular invasion compared with the other patients (55.7% *vs.* 34.5%, P<0.001; 76.4% *vs.* 42.3%, P<0.001; respectively). The mean number of MLNs was also higher in the N1b group than in the other patients (9.3 *vs.* 1.2, P<0.001). All patients with N1b disease underwent total thyroidectomy with CCND and selective lymph node dissection at initial surgery.

The clinicopathological factors associated with N1b disease (Table 5)

Logistic regression analysis was performed to analyze the clinicopathological characteristics associated with N1b disease. In univariate analysis, factors related to N1b disease were age of 10s to 30s [HR (95% CI), 1.457 (1.121–1.894), P=0.005], male sex [HR (95% CI), 1.784 (1.348–2.361), P<0.001], tumor size >0.65 cm [HR (95% CI), 2.503 (1.935–3.237), P<0.001], presence of capsular invasion [HR (95% CI), 4.425 (3.280–5.971), P<0.001], and presence of multifocality [HR (95% CI), 2.390 (1.846–3.093), P<0.001]. In the multivariate analysis, the independent factors associated with N1b disease were age of 10s to 30s [HR (95% CI), 1.564 (1.192–2.050), P<0.001], male sex [HR (95% CI), 1.721 (1.290–2.297), P<0.001], tumor size >0.65 cm [HR (95% CI), 1.816 (1.393–2.368), P<0.001], presence of capsular invasion [HR (95% CI), 3.738 (2.751–5.080), P<0.001], and presence of multifocality [HR (95% CI), 2.104 (1.615–2.742), P<0.001].

Discussion

AS has been suggested as an alternative to initial thyroidectomy for patients with PTMC (4). Despite the many advantages of AS, and the fact that rescue surgery can

Table 4 The clinicopathologic characteristics of the patients without lateral neck node metastasis (N0 or N1a) and those with lateral neck node metastasis (N1b)

Variables	N0 or N1a (n=5,083)	N1b (n=246)	P value
Age (years)	46.4±11.7 [13–80]	44.9±13.1 [18–82]	
Age			0.066
<55:≥55 years	3,796 (74.7):1,287 (25.3)	182 (87.0):64 (26.0)	0.806
<40:≥40 years	1,570 (30.9):3,513 (69.1)	97 (39.4):149 (60.6)	0.005
Sex (female:male)	4,080 (80.3):1,003 (19.7)	171 (69.5):75 (30.5)	<0.001
Tumor size (cm)	0.62±0.20 [0.08–1.00]	0.72±0.20 [0.10–1.00]	<0.001
Tumor size			<0.001
≤0.65 cm	3,598 (70.8)	121 (49.2)	
>0.65 and ≤1 cm	1,485 (29.2)	125 (50.8)	
Multifocality			<0.001
No	3,331 (65.5)	109 (44.3)	
Yes	1,752 (34.5)	137 (55.7)	
Capsular invasion			<0.001
No	2,934 (57.7)	58 (23.6)	
Yes	2,149 (42.3)	188 (76.4)	
Nodal status			
Metastasis			<0.001
No	2,948 (58.0)	0 (0.0)	
Yes	2,135 (42.0)	246 (100.0)	
Number of MLNs	1.2±2.2 [0–30]	9.3±6.5 [1–32]	<0.001
The nodal risk group			<0.001
Higher-risk N1	261 (5.1)	154 (62.6)	
Lower-risk N	4,822 (94.9)	92 (37.4)	
Thyroidectomy			<0.001
Total thyroidectomy	2,304 (45.3)	246 (100.0)	
Unilateral lobectomy	2,632 (51.8)	0 (0.0)	
Isthmusectomy	147 (2.9)	0 (0.0)	

Data are presented as mean ± SD [min–max] or n (%). Higher-risk N1 group: patients with more than five MLNs; lower-risk N group: patients with no or less than equal to five MLNs. MLN, metastatic lymph node.

be offered safely in the event of tumor progression or novel metastasis, the risk of disease progression is a major concern for AS in comparison with immediate surgery (4,23). It is currently difficult for clinicians to predict which patients will progress and which patients will be stable during AS. Ito *et al.* reported in an observational trial that young age or pregnancy might be factors that promote tumor growth during AS (3,4,7). Unfortunately, no definite clinical features or molecular abnormality in isolation can reliably differentiate whether or not PTMC will progress in patients under AS (1,5).

Enlargement of the primary tumor can be easily tracked using high-resolution ultrasonography; however, lymphatic spread is difficult to detect with current imaging studies

Table 5 The clinicopathological factors associated with N1b disease

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age				
≥40s		Ref.		Ref.
10s to 30s	1.457 (1.121–1.894)	0.005	1.564 (1.192–2.050)	<0.001
Sex				
Female		Ref.		Ref.
Male	1.784 (1.348–2.361)	<0.001	1.721 (1.290–2.297)	<0.001
Tumor size				
≤0.65 cm		Ref.		Ref.
>0.65 and ≤1 cm	2.503 (1.935–3.237)	<0.001	1.816 (1.393–2.368)	<0.001
Capsular invasion				
No		Ref.		Ref.
Yes	4.425 (3.280–5.971)	<0.001	3.738 (2.751–5.080)	<0.001
Multifocality				
No		Ref.		Ref.
Yes	2.390 (1.846–3.093)	<0.001	2.104 (1.615–2.742)	<0.001

HR, hazard ratio; CI, confidence interval; ref., reference.

(8,9,13,23). In addition, occult lymph node metastases in the central compartment are common among patients with PTCs, and nodal risk factors, including the number of metastatic nodes, the size of metastatic foci, and the presence of extra-nodal extension, are difficult to determine without pathological confirmation accompanied by surgery (10-12,23).

The ATA proposed a modified three-tiered initial risk stratification system to predict the risk of structural disease recurrence after initial surgery (1). One of the factors that aggravate the risk from a low level to an intermediate level is the presence of more than five MLNs, which increases the structural recurrence rate by up to 19% (1). With regard to the nodal status, Randolph *et al.* suggested the concept of higher-risk and lower-risk N1 disease based on the size and number of MLNs; higher-risk N1 disease was defined by more than five MLNs and showed a recurrence rate >20% in their study (17). According to recent guidelines, RAI therapy is recommended for patients with higher-risk N1 disease (1,18). The site of metastasis also affects the treatment policy for PTMC. Whereas lobectomy alone is sufficient for most PTMCs, N1b disease with the presence of lateral neck lymph node metastases requires RAI therapy following total thyroidectomy with selective neck node dissection (1,18,24,25). Based on existing knowledge of how nodal factors affect the prognosis and treatment of PTC, we defined high-risk nodal disease as PTMC with higher-risk N1 status and/or N1b status in this study. We analyzed a large volume of postoperative retrospective pathologic data to determine the incidence and risk factors for high-risk nodal disease among patients with PTMC.

In our cross-sectional study of 5,329 patients with PTMC, 9.5% (507/5,329) of the patients had at least one of our two defining characteristics for high-risk nodal disease [higher-risk N1 disease (n=415, 7.8%) and/or N1b disease (n=246, 4.6%)]. Young age, male sex, tumor size >0.65 cm, capsular invasion, and multifocality were each associated with high-risk nodal disease.

In the present study, younger age showed a high correlation with high-risk nodal disease. The HR of higher-risk N1 disease was 3.757 for patients in their 10s and 20s and 1.827 for patients in their 30s and 40s relative to patients in their 50s or older in a multivariate analysis. In the multivariate analysis for N1b disease, the HR was 1.564

for patients 10s to 30s of age relative to patients older than 40s. Similarly, Ito *et al.* found that young age (<40 years) was an independent predictor of PTMC progression including novel nodal metastases during AS (3). Shukla *et al.* demonstrated that younger age was associated with higher numbers of total positive nodes in PTC (26); the HR of lymph node metastasis was 7.19 for patients aged 0–10 years, 3.45 for patients aged 11–20 years, and 2.28 for patients aged 21–30 years relative to patients >30 years of age. Liu *et al.* and others suggested that young age (<45 or <55 years) was a risk factor for central lymph node metastasis (27-29).

In our study, male sex was an independent risk factor associated with high-risk nodal disease in PTMC without ETE (HR, 3.236 for higher-risk N1 disease; HR, 1.721 for N1b disease). In the study of Lee *et al.*, PTC showed more nodal involvement, more lymph vascular invasion, and more recurrence in males than in females (30). In a subgroup analysis of PTMC from that study, sex was not associated with a difference in recurrence; however, males had more nodal involvement and lymph vascular invasion than females. Gui *et al.* also mentioned male gender as a risk factor for lymph node metastases, a finding which was supported by other studies (27-29,31).

Tumor size is identified as a prognostic factor in multiple studies and is also related to lymph node metastasis (1,27,28,31-34). However, the cutoff values of primary tumor size used to predict lymph node metastasis in PTMC vary. Previous studies have suggested several cutoff values ranging from 0.5 to 0.575 cm to predict nodal metastasis (27,28,31). In our analysis, we concluded that 0.65 cm was the proper cutoff value to screen for high-risk nodal disease in PTMC without ETE. Tumor size >0.65 cm was associated with HRs of 1.816 for higher-risk N1 disease and 1.816 for N1b disease. It seems to be useful to divide the size of cancer based on 7 mm because it is impossible to measure less than a millimeter when performing ultrasound examination for clinicians.

Thyroid capsular invasion alone is no longer reflected in tumor-node-metastasis (TNM) staging from the 8th edition of the American Joint Committee on Cancer (AJCC) manual (34). In contrast, Sorrenti *et al.* suggested that capsular invasion was one of the risk factors for recurrence in PTC (35). However, we found that thyroid capsular invasion was related to nodal metastasis, and it was an independent risk factor for both higher-risk N1 disease (HR, 2.523) and N1b disease (HR, 3.738). These findings are consistent with previous research. Capsular invasion was found to be a risk factor for central lymph node metastasis in PTMC with detectable findings by preoperative ultrasonography (36,37). Capsular invasion confirmed by ultrasonography or pathology was also suggested as an independent risk factor for lateral neck lymph node metastasis in PTMC (38,39). Contact of more than 25% with the adjacent thyroid capsule in ultrasonography was shown to be an independent predictor of lateral neck lymph node metastasis in PTMC (38). Therefore, careful observation is necessary for patients when ultrasonography findings are suspicious for capsular invasion during AS.

Many reports suggest that multifocality is related to increased lymph node metastasis in PTC (27,28,31,40,41). In our multivariate analysis of PTMC without ETE, the presence of multifocality increased the risks of higher-risk N1 disease by 2.342-fold and N1b disease by 2.104-fold. Although above multifocality information was confirmed in the final histopathological examination, determining the presence of multifocality before surgery seems to be helpful in predicting the patient's nodal risk. Because preoperative ultrasonography is useful for detecting cancer as small as 2 mm (42,43) and suspicious lesions with a size of 1 mm could be diagnosed through sonography-guided fine-needle aspiration biopsy depends on investigator's performance (44).

PTMCs without ETE are known as suitable candidates for AS (3,4,6); however, PTMCs with high-risk nodal disease have higher recurrence rates and require total thyroidectomy or postoperative RAI therapy (1,18). Considering the progression of the tumor during AS, it should be noted that novel high-risk nodal disease may develop over time during the observational period. Therefore, a cautious observation strategy is necessary for AS in patients with the risk factors of young age, male sex, tumor size >0.65 cm, capsular invasion, and multifocality, all of which are associated with high-risk nodal disease in PTMC.

Our research has several limitations. This study is cross-sectional, retrospective, and reflects only patients that received surgical treatment at our institution, so it is improper to estimate the rates of novel events over time during the observation period. Future prospective, multicenter studies with ethnically diverse populations are needed. Since the capsular invasion, multifocality, and cancer size presented as predictive factors in our research were obtained through pathologic examination, it may be difficult to apply directly to preoperative ultrasonography.

In addition, the size of metastatic foci in the lymph nodes was not considered in our study. Therefore, an analysis of the predictable features in preoperative stage related to this nodal risk factor will help identify patients that require close observation during AS.

Conclusions

Young age, male sex, tumor size >0.65 cm, capsular invasion, and multifocality increase the risk of having more than five MLNs (higher-risk N1 disease) or lateral neck lymph node metastasis (N1b disease), even in PTMC without ETE. Judicious follow-up considering these characteristics is necessary during AS for patients with PTMC.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, the Catholic University of Korea (No. KC22WISI0219) and individual consent for this retrospective analysis was waived.

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