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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Superior Located Papillary Thyroid Microcarcinoma is a Risk Factor for Lateral Lymph Node Metastasis

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ABSTRACT

Background. It is important to identify prognostic factors for lateral lymph node metastasis (LLNM) in papillary thyroid microcarcinoma (PTMC) because they determine the extent of surgery. Several similarly designed studies have investigated predictors of LLNM, but with no more than 1000 cases. In addition, there are no recommendations or guidelines covering the differences in risk by tumor location. This study is the largest, using a papillary thyroid microcarcinoma population with 2967 patients. The purpose of this study is to address predictive factors of LLNM, focusing on lesion location.

Patients and Methods. We retrospectively reviewed the data of 2967 PTMC patients who underwent total thyroidectomy and central neck dissection and/or lateral neck dissection (unilateral or bilateral) between January 1997 and June 2015.

Results. On multivariate analysis, superior lesion [adjusted odds ratio (OR) 3.32, $p < 0.000$], male gender (adjusted OR 1.39, $p = 0.0047$), age under 45 years (adjusted OR 1.42, $p = 0.015$), and central lymph node metastasis (adjusted OR 3.40, $p < 0.000$) were significant predictors of high-risk LLNM. Superior lesion [hazard ratio (HR) 2.32, $p = 0.005$] and central lymph node metastasis (CLNM, HR 7.12, $p < 0.000$) were significant risk factors for locoregional recurrence (LRR). To reduce the effect of selection bias, we performed propensity score matching analysis with regard to tumor location. With a total of 1138 patients with matched data and 569 patients for each location, superior lesion (adjusted OR 3.17, $p < 0.000$), age under 45 years (adjusted OR 1.73, $p = 0.005$), and CLNM (adjusted OR 2.77, $p < 0.000$) were independent predictive factors of LLNM. Superior lesion (HR 2.28, $p = 0.04$) and CLNM (HR 5.32, $p = 0.001$) were significant risk factors for LRR.

Conclusions. In addition to young age, male gender, and CLNM identified in previous studies, meticulous assessment for LLNM is required in PTMC patients when lesions are located in the superior pole of the thyroid during preoperative evaluation or postoperative follow-up, because superior located papillary microcarcinoma is a risk factor for LLNM and LRR.

Papillary thyroid microcarcinoma (PTMC) is a thyroid cancer smaller than 1 cm maximum.[1–5] PTMC is a less aggressive type of cancer that is curable with surgical or medical therapy.[5–14] The incidence of PTMC has increased recently because of early detection,[7,8,15] including in Korea. Previous studies reported that approximately 3.1–18.2% of patients with PTMC have lymph node metastasis (LNM), and 21% of these patients have lateral lymph node metastasis (LLNM).[3,16–18] Identifying LNM preoperatively is important because it determines the extent of surgery required to prevent reoperation and subsequent complications.[7,8] LNM is a proven predictor for locoregional recurrence (LRR) in PTMC patients.[16] Several similarly designed studies have investigated predictors of LLNM, but with no more than 1000 cases.[7,8,10–14] The aim of this study is to address predictive factors of LLNM, focusing on lesion location, in a large group of patients with PTMC at a tertiary center.

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TABLE 1 Baseline clinicopathologic characteristics of 2967 PTMC patients who underwent total thyroidectomy and central neck dissection and/or lateral neck dissection (unilateral or bilateral)

Clinicopathologic characteristic	No. of patients (%)
Age (years)	
Mean ± SD	47.57 ± 10.39
≥ 45	1846 (62.22)
< 45	1121 (37.78)
Sex, *n* (%)	
Male	541 (18.23)
Female	2426 (81.77)
Extent of surgery, *n* (%)	
TT + CND	2967 (100.0)
TT + LND	231 (7.80)
Location, *n* (%)	
Superior pole	569 (19.18)
Others	2398 (80.82)
Tumor size (cm)	
Mean ± SD	0.63 ± 0.21
0.5 ≤	1111 (37.45)
0.5 >	1856 (62.55)
CLT, *n* (%)	
Absent	2133 (71.89)
Present	834 (28.11)
Gross ETE, *n* (%)	
Yes	235 (7.92)
No	2732 (92.08)
CLNM, *n* (%)	
Absent	1690 (56.96)
Present	1277 (43.04)
LLNM, *n* (%)	
Absent	2736 (92.21)
Present	231 (7.79)
Recurrence, *n* (%)	
Absent	2881 (98.29)
Present	50 (1.71)
T stage[b], *n* (%)	
T1	1408 (47.46)
T3	1474 (49.70)
T4	85 (2.86)
N stage, *n* (%)	
N0	1459 (49.20)
N1a	1277 (43.04)
N1b	231 (7.79)
BRAF[a] positivity	
No	175 (19.42)
Yes	726 (80.58)

PTMC papillary thyroid carcinoma, *TT* total thyroidectomy, *Uni* unilateral, *Bi* bilateral, *SD* standard deviation, *LND* lateral neck dissection including modified radical neck dissection and selective neck dissection, *CND* central neck dissection, *ETE* extrathyroidal extension, *CLT* chronic lymphocytic thyroiditis, *CLNM* central lymph node metastasis, LLNM lateral lymph node metastasis

[a]*BRAF* mutation analysis was performed starting in 2008

[b]T stage determined in accordance with the 7th edition of the *AJCC Cancer Staging Manual and the Future of TNM*[10]

PATIENTS AND METHODS

Patient Selection

A retrospective cohort study was conducted with data collected between January 1997 and June 2015 at the Thyroid Cancer Center of Samsung Medical Center, a tertiary referral center in Korea. The Institutional Review Board at Samsung Medical Center approved this study of 2967 PTMC patients who underwent total thyroidectomy and central neck dissection and/or lateral neck dissection (unilateral or bilateral). Patients who met the following criteria were excluded from analysis: age younger than 20 or older than 80 years, previous history of thyroidectomy, non-PTC carcinoma (follicular/medullary/anaplastic), mixed-type PTC, minor variants of PTC, lobectomy, total thyroidectomy without central neck dissection (CND), tumor size > 1 cm, multiplicity, bilaterality, presence of distant metastasis, or follow-up duration less than 6 months [residual tumor or lymph node (LN) detected within 6 months after initial surgery, reoperation within 6 months after initial surgery, or loss to follow-up within 6 months because of withdrawal or death]. All patients diagnosed with thyroid cancer preoperatively by fine-needle aspiration (FNA) or core-needle biopsy (CNB) underwent surgery.

The preoperative work-up was performed through ultrasonography (US) and neck computed tomography (CT). Suspicious lesions were diagnosed preoperatively by FNA or CNB. If a patient had palpable LNs or suspicious metastatic LNs on preoperative US, FNA or washout thyroglobulin level (TG) was performed.

TABLE 2 Relationships between clinicopathological characteristics and LLNM in 2967 patients who underwent total thyroidectomy and central neck dissection and/or lateral neck dissection (unilateral or bilateral)

	LLNM, no. (%)			Multivariate analysis	
	Absent	Present	*p* value	Adjusted OR (95% CI)	*p* value
Total no.	2736 (92.20)	231 (7.80)			
Age, years					
< 45	1006	115 (10.30)	Ref	1.42 (1.07–1.88)	0.015
≥ 45	1730	116 (6.30)	< 0.001	Ref	Ref
Sex					
Male	481	60 (11.10)	0.002	1.39 (1.00–1.92)	0.047
Female	2255	171 (7.00)	Ref	Ref	Ref
Location					
Superior pole	477	92 (16.20)	< 0.001	3.32 (2.49–4.44)	< 0.001
Others	2259	139 (5.80)	Ref	Ref	Ref
Tumor size (cm)					
0.5 ≤	1050	61 (5.50)	Ref	Ref	Ref
0.5 >	1686	170 (9.20)	< 0.001	1.34 (0.97–1.83)	0.072
CLT					
Absent	1961	172 (8.10)	Ref		
Present	775	59 (7.10)	0.366		
Gross ETE					
Yes	210	25 (10.60)	0.091		
No	2526	206 (7.50)	Ref		
CLNM					
Absent	1625	65 (3.80)	Ref	Ref	Ref
Present	1111	166 (13.00)	< 0.001	3.40 (2.50–4.64)	< 0.001
BRAF[a] positivity					
Yes	663	63 (8.70)	0.116		
No	153	22 (12.60)			

LLNM lateral lymph node metastasis, *PTMC* papillary thyroid carcinoma, *ETE* extrathyroidal extension, *CLT* chronic lymphocytic thyroiditis, *CLNM* central lymph node metastasis, *OR* odds ratio, *CI* confidence interval, *Ref* reference

[a]*BRAF* mutation analysis was performed starting in 2008

Surgical Methods

In our center, surgical strategies have been performed in accordance with American Thyroid Association Guidelines.[11] Total thyroidectomy was performed when extrathyroidal extension (ETE), multiplicity, bilaterality, or abnormal lymphadenopathy was found during preoperative or intraoperative examination. Therapeutic CND was conducted in patients who had abnormal lymphadenopathy during preoperative or intraoperative examination. The central compartment LNs consist of the level VI LNs (pretracheal, prelaryngeal, and paraesophageal LNs), which include the LNs from the hyoid bone superior to the suprasternal notch inferiorly and laterally from the medial border of the common carotid artery to the midline of the trachea. For patients diagnosed with metastatic thyroid cancer in the lateral neck, lymph node dissection, including modified radical neck dissection (MRND) and selective neck dissection (SND), was carried out. Therapeutic MRND was performed only in patients with cytologically confirmed LLNM preoperatively or intraoperatively. MRND was defined as neck dissection of levels II–V, sparing the sternocleidomastoid muscle, spinal accessory nerve, and internal jugular vein. Prophylactic MRND was not performed routinely.

Histopathological Examination

For final pathological diagnosis, at least two expert pathologists reviewed the surgical specimens. Only conventional PTC populations were included in the study, and the following factors were assessed: primary tumor size (longest diameter of the largest lesion), cell type of main lesion, location, multifocality, ETE, margin status, lymphovascular invasion, underlying thyroid disease such as thyroiditis, and LNM. Thyroid cancer stage was

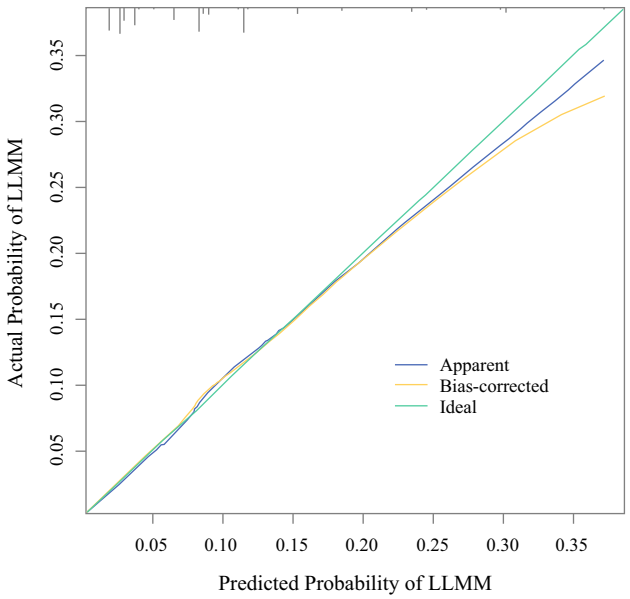


FIG. 1 Calibration plot of the nomogram for predicting LLNM in PTC patients

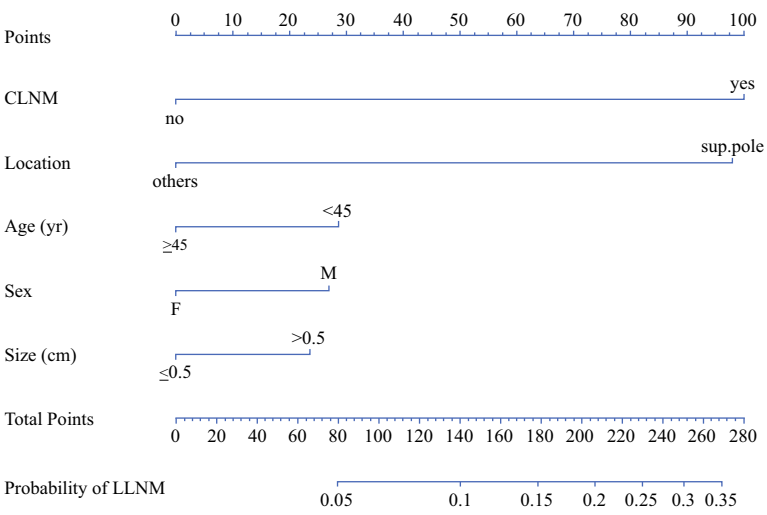
determined following the guidelines of the American Joint Committee on Cancer.[10]

Postoperative Follow-Up

All patients underwent regular follow-up at 6–12-month intervals with physical examination, ultrasonography (US), computed tomography (CT), iodine-131 scans, and serum TG measurement. All patients were treated with levothyroxine for thyroid-stimulating hormone (TSH) suppression therapy postoperatively with or without radioactive iodine (RAI) ablation. According to American Thyroid Association guidelines, RAI was performed based on patient stage and risk factors at 4–12 weeks after surgery,[19] but the final decision was made by the doctor or patient. On completion of RAI treatment, regular follow-up was resumed. The date of last follow-up was defined by loss to follow-up, withdrawal, recurrence, or death. Patients with suspicious recurrence or distant metastasis were evaluated using US-guided fine-needle aspiration biopsy with or without washout TG level and/or computed tomography (CT) or positron emission tomography-CT. Recurrence was considered as the presence of tumor or metastatic LN on FNAC during follow-up or on final pathology report after reoperation. Recurrence-free survival (RFS) was defined as time from surgery to date of detection of first recurrence.

Variables

The preoperative images of the entire patient were reviewed to describe the tumor location. The locations were mainly described based on US images; however, CT findings were considered if US images were vague or unavailable. In our institution, the thyroid is subdivided into three anatomical portions on formal reading of US images: upper, middle, and lower. In this study, we focused on whether a main lesion was located in the upper pole or not, so locations were indicated by two categories: superior and other. ETE was evaluated based on both postoperative pathologic report and intraoperative findings according to operation record. Tumor sizes were categorized into two groups: > 0.5 cm and ≤ 0.5 cm. LRR was considered to have developed when metastatic LN or tumor was present on cytology by aspiration biopsy.



CLNM	Points
no	0
yes	100

Location	Points
others	0
sup.pole	98

Age(yr)	Points
≥45	0
<45	29

Sex	Points
F	0
M	27

Tumor size(cm)	Points
≤0.5	0
>0.5	24

Total Points	Predicted Value
79	0.05
140	0.1
178	0.15
207	0.2
230	0.25
251	0.3
269	0.35

FIG. 2 Nomogram for predicting LLNM in PTMC patients

TABLE 3 Cox proportional-hazards regression analysis for relationships between clinicopathological characteristics and locoregional recurrence in 2967 patients who underwent total thyroidectomy and central neck dissection and/or lateral neck dissection (unilateral or bilateral)

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age, years				
> 45		Ref		
≤ 45	1.45 (0.83–2.54)	0.187		
Sex				
Male		0.645		
Female	1.18 (0.59–2.36)	Ref		
Location				
Superior pole	2.28 (1.27–4.09)	0.006	2.32 (1.30–4.17)	0.005
Others		Ref	Ref	
Tumor size (cm)				
0.5 ≤	2.31 (1.18–4.52)	Ref	1.72 (0.88–3.38)	Ref
0.5 >		0.014		0.114
CLT				
Absent		Ref		
Present	0.86 (0.45–1.65)	0.657		
Gross ETE				
Yes	1.99 (0.85–4.69)	0.114		
No		Ref		
CLNM				
Absent		Ref	Ref	< 0.001
Present	7.63 (3.58–16.25)	< 0.001	7.12 (3.32–15.24)	
BRAF positivity				
Yes	8.16 (0.43–154.36)	0.162		
No		Ref		

LLNM lateral lymph node metastasis, *PTMC* papillary thyroid carcinoma, *ETE* extrathyroidal extension, *CLT* chronic lymphocytic thyroiditis, *CLNM* central lymph node metastasis, *OR* odds ratio, *CI* confidence interval, *Ref* reference

**BRAF* mutation analysis was performed starting in 2008

Statistical Analysis

Statistical analysis was executed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). The association of potential risk factors with outcomes (LLNM, LRR) was tested by logistic regression analysis. Variables with *p* value less than 0.05 on univariate analysis were included in multivariate analysis. The clinically important factor of location was included in all multivariate analysis regardless of *p* value on univariate analysis. We performed only univariate analysis for *BRAF* due to the small sample size. The association of potential risk factors with outcomes (LRR) was tested by Cox proportional-hazards regression analysis, and clustered Cox proportional-hazards regression analysis was applied to matched paired data. To reduce the effect of selection bias, we performed propensity score matching analysis between the superior group and other group. Generalized estimating equations were used to analyze matched paired data. Propensity scores were estimated using a logistic regression model of the following covariates: patient sex and age, CLNM, tumor size, multiplicity, and gross ETE. *p* values were calculated using Chi square test for original data and McNemar's test for matched paired data.

RESULTS

Clinicopathologic Characteristics of 2967 PTMC Patients

Among 2967 PTMC patients, 541 (18.23%) were male and 2426 (81.77%) were female (Table 1). The mean age was 47.57 years. Preoperative imaging studies showed that 2519, 217, and 231 patients were clinical stage N0, N1a, and N1b, respectively. Total thyroidectomy and central neck dissection and therapeutic modified radical neck

TABLE 4 Propensity score matching for relationships between clinicopathological characteristics and LLNM in 1138 patients who underwent total thyroidectomy and central neck dissection and/or lateral neck dissection (unilateral or bilateral)

	LLNM, no. (%)			Multivariate analysis	
	Absent	Present	*p* value	Adjusted OR (95% CI)	*p* value
Age, years					
< 45	370	67 (15.30)	Ref		Ref
≥ 45	642	59 (8.40)	< 0.001	1.73 (1.18–2.53)	0.005
Sex					
Male	160	26 (14.00)	0.162		
Female	852	100 (10.50)	Ref		
Location					
Superior pole	477	92 (16.20)	< 0.001	3.17 (2.09–4.81)	< 0.001
Others	535	34 (6.00)	Ref		Ref
Tumor size (cm)					
0.5 ≤	367	39 (9.60)	Ref		Ref
0.5 >	645	87 (11.90)	0.233	1.328 (0.98–1.80)	0.066
CLT					
Absent	713	98 (12.10)	Ref		Ref
Present	299	28 (8.60)	0.081	0.67 (0.43–1.06)	0.088
Gross ETE					
Yes	91	17 (15.70)	0.128		
No	921	109 (10.60)	Ref		
CLNM					
Absent	609	43 (6.60)	Ref		Ref
Present	403	83 (17.10)	< 0.001	2.77 (1.87–4.10)	< 0.001
BRAF[a] positivity					
Yes	248	38 (13.30)	0.311		
No	59	13 (18.10)	Ref		

LLNM lateral lymph node metastasis, *PTMC* papillary thyroid carcinoma, *ETE* extrathyroidal extension, *CLT* chronic lymphocytic thyroiditis, *CLNM* central lymph node metastasis, *OR* odds ratio, *CI* confidence interval, *Ref* reference

[a]*BRAF* mutation analysis was performed starting in 2008

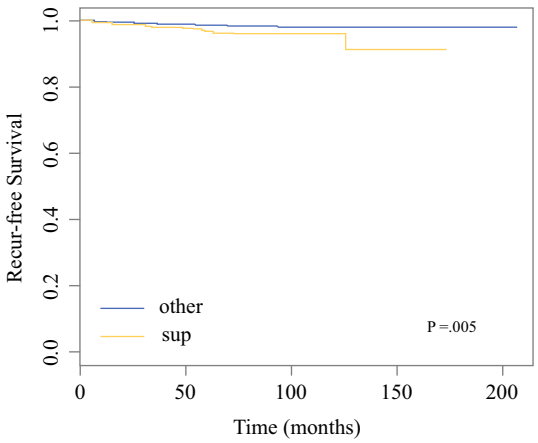


FIG. 3 Recurrence free survival curve in 2967 PTMC patients

dissection (MRND) or selective neck dissection (SND) were performed in 2967 (100%) patients and in 231 (7.80%) patients, respectively, and bilateral MRND was performed in 4 (0.13%) patients. Superior pole located PTMC occurred in 569 patients (19.18%). The mean tumor size was 0.63 cm, with 1856 (62.55%) patients having a tumor smaller than 0.5 cm and 1111 (37.45%) a tumor larger than 0.5 cm. Gross ETE occurred in 235 (7.92%), CLNM in 1277 (43.00%), LLNM in 231 (7.80%), and recurrence in 50 (1.70%) over a median follow-up of 62.4 months. In the younger group aged under 45 years, 115 (10.30%) had LLNM. This analysis showed that younger patients had relatively higher risk of LLNM than the older group. Because *BRAF* mutation analysis was not performed until 2008 in our institution, *BRAF* status was available for only 901 (30.40%) patients, among whom the *BRAF* positivity rate was 80.60% (Table 1). According to the tumor–node–metastasis (TNM) stage classification, 1408 (47.50%) patients had T1 cancer lesions and 1474 (49.70%) patients had T3 lesions. Concerning N stage, central LNM (N1a) and LLNM (N1b) were found in 1277 (38.90%) and 231 (9.30%) patients, respectively.

TABLE 5 Clustered Cox proportional-hazards regression analysis of matched paired data for relationships between clinicopathological characteristics and locoregional recurrence in 1138 patients who underwent total thyroidectomy and central neck dissection and/or lateral neck dissection (unilateral or bilateral)

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age, years				
< 45		0.080		
≥ 45	2.10 (0.92–4.82)	Ref		
Sex				
Male		0.963		
Female	1.03 (0.35–3.01)	Ref		
Location				
Superior pole		0.042	2.28 (1.04–5.02)	0.040
Others	2.24 (1.03–4.88)	Ref		Ref
Tumor size (cm)				
0.5 ≤		Ref	2.62 (0.89–7.77)	Ref
0.5 >	3.29 (1.16–9.68)	0.031		0.082
CLT				
Absent		Ref	1.508 (0.910–2.499)	Ref
Present	1.05 (0.47–2.34)	0.904		0.111
Gross ETE				
Yes		0.130		
No	2.26 (0.79–6.50)	Ref		
CLNM				
Absent		Ref	5.32 (1.96–14.39)	Ref
Present	5.85 (2.18–15.73)	< 0.001		0.001
BRAF[a] positivity	N/A	N/A		

LLNM lateral lymph node metastasis, *PTMC* papillary thyroid carcinoma, *ETE* extrathyroidal extension, *CLT* chronic lymphocytic thyroiditis, *CLNM* central lymph node metastasis, *OR* odds ratio, *CI* confidence interval, *Ref* reference

[a]*BRAF* mutation analysis was performed starting in 2008

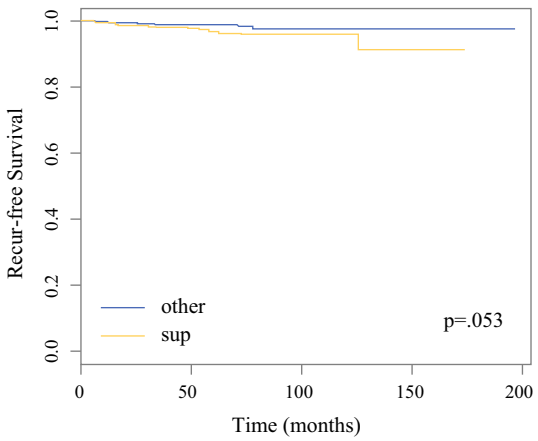


FIG. 4 Recurrence free survival curve in 1138 propensity score-matched PTMC patients

Univariate and Multivariate Predictive Factors of Lateral Lymph Node Metastasis

On univariate analysis of 2967 PTMC patients, superior lesion (adjusted OR 3.14, $p < 0.001$), male gender (adjusted OR 1.65, $p = 0.002$), age under 45 years (adjusted OR 1.71, $p < 0.001$), CLNM (adjusted OR 3.74, $p < 0.001$), and tumor size > 0.5 cm (adjusted OR 1.74, $p < 0.001$) were significant predictive factors for LLNM.

On multivariate analysis, superior lesion (adjusted OR 3.32, $p < 0.001$), male gender (adjusted OR 1.39, $p = 0.047$), age under 45 years (adjusted OR 1.42, $p = 0.015$), and CLNM (adjusted OR 3.40, $p < 0.001$) were significant predictors for high risk of LLNM (Table 2). Among 231 patients with LLNM, there were 65 (28.00%) patients who had LLNM without CLNM, defined as skip metastasis.

Nomogram for Predicting LLNM in PTMC Patients

To develop and validate a nomogram, five important predictors of LLNM were included in multiple logistic regression analysis. These factors were proportionally assigned as points on a scale from 0 to 100 based on a calibration plot estimated using 1000 bootstrap samples. The mean absolute error was 0.003, and an apparent line in

the calibration plot for predicting LLNM was very close to an ideal line. As an example of calculating the predicted probability of LLNM in a PTMC patient, a 40-year-old man with 0.70-cm PTMC with superior location and CLNM has a 35–40% chance of LLNM (Fig. 1).

Cox Proportional-Hazards Regression Analysis for Locoregional Recurrence

On univariate analysis of LRR, superior lesion (HR 2.28, $p = 0.006$), CLNM (HR 7.63, $p < 0.001$), and tumor size > 0.5 cm (HR 2.31, $p = 0.014$) were significantly associated with LRR (Fig. 2).

On multivariate analysis, superior lesion (HR 2.32, $p = 0.005$) and CLNM (HR 7.12, $p < 0.001$) were significant risk factors for LRR (Table 3).

Propensity Score Matching Analysis for Lateral Lymph Node Metastasis

To reduce the effect of selection bias, we performed propensity score matching analysis for location (Table 4). With a total of 1138 patients with matched data and 569 patients for each location, superior pole lesion (adjusted OR 3.04, $p < 0.001$), age under 45 years (adjusted OR 1.97, $p < 0.001$), and CLNM (adjusted OR 2.92, $p < 0.001$) were related to high prevalence of LLNM on univariate analysis (Fig. 3).

On multivariate analysis, upper lesion (adjusted OR 3.17, $p < 0.001$), age under 45 years (adjusted OR 1.73, $p = 0.005$), and CLNM (adjusted OR 2.77, $p < 0.001$) were independent predictive factors for LLNM (Table 4).

On univariate analysis of LRR, superior lesion (HR 2.24, $p = 0.042$), CLNM (HR 5.85, $p < 0.001$), and tumor size > 0.5 cm (HR 3.29, $p = 0.031$) were significantly associated with LRR.

On multivariate analysis, superior lesion (HR 2.28, $p = 0.040$) and CLNM (HR 5.32, $p = 0.001$) were significant risk factors for LRR (Table 5).

DISCUSSION

We analyzed data on a total of 2967 PTMC patients. Our results demonstrated that 231 patients had LLNM, and patients with superior pole located thyroid cancer had high probability of LLNM and LRR. Many studies report that age, sex, tumor size, and CLNM were significant predictive factors for LLNM in PTMC patients.[7–9,12–14,20–22] Our research is almost consistent with the results of these previous studies. However, tumor size and sex were not correlated with LLNM on multivariate analysis with propensity score matching. Especially with respect to tumor size, we assume that the anatomical position may have a greater effect on LLNM than the size in case of small cancers and that cancer spreads in its early stages because of its genetic characteristics or other factors such as host or environmental factors that may have affected LLNM (Fig. 4).

Previous studies indicated that pathologic ETE is a prognostic factor for LLNM.[7,23] However, according to recently published updated American Joint Committee on Cancer (AJCC) guidelines, microscopic ETE identified only on histological examination is not clinically important, although gross ETE is critically important. The eighth edition of the AJCC guidelines defines gross ETE as a finding based on radiologic and/or clinical evidence of a macroscopic tumor extending outside the thyroid.[24] For this reason, operation records of all patients in this study were reviewed. We evaluated gross ETE according to intraoperative findings of operation records. Gross ETE was not significantly associated with LLNM on univariate and multivariate analysis of logistic regression or propensity score matching. For small cancers, such as PTMC, finding gross ETE in the actual operative field is unlikely, or there is a probability that intraoperative findings may be unclear or there could be discrepancy between surgeons. Based on this, anatomical position may be more important than gross ETE, especially for PTMC patients. Considering the morphology of the thyroid gland, the superior portion has a relatively small amount of tissue, so tumor burden is higher than that for a same-sized tumor in the lower portion. This increased tumor burden might be assumed to result in earlier pathological extracapsular invasion or LLNM. In addition, a previous study demonstrated that lymphatic flow along the superior thyroid artery facilitates metastasis of tumor cells, illustrating that location affects LLNM.[25]

According to guidelines from the Japanese Thyroid Association and American Thyroid Association,[11] lesions adjacent to the trachea are recommended for operation regardless of size; however, no recommendations or guidelines cover differences in risk by tumor location. To the best of the authors' knowledge, this study is the largest to date to show risk factors for LLNM in a PTMC with nearly 3000 patients, especially for tumor location. When deciding surgery on PTMC patients, we focused on providing additional evidence for surgical decisions for this population, in addition to previously proven predictive factors, because the current PTMC guidelines recommending active surveillance might have overlooked potential dangers. We showed that superior located tumors metastasized more easily to the lateral lymph nodes and require meticulous preoperative evaluation or careful observation after surgery in outpatient clinic. Thus, even small lesions in the superior pole, LLNM, or CLNM should

be carefully evaluated using various imaging modalities and diagnostic examinations such as FNAC or CNB[26,27] rather than by observation. Surgical treatment is recommended if results are Bethesda V or above.

This study had several limitations. The first is a statistical limitation because this was a retrospective study conducted in a single center. Second, we performed only univariate analysis for *BRAF* mutation status due to the small sample size (67% of *BRAF* data were default values) because *BRAF* mutation analysis was not performed until 2008 at our institution. Although several studies have demonstrated that *BRAF* mutations are related to aggressive behavior of PTC, other studies have shown that *BRAF* mutations are not a predictive factor for LLNM.[28,29] Third, the intraoperative findings could be unclear or vary depending on surgeon in cases of PTMC.

CONCLUSIONS

In addition to young age, male gender, and CLNM identified in previous studies, meticulous preoperative assessment and closer follow-up for LLNM are required in PTMC patients when lesions are located in the superior pole of the thyroid because superior located PTMC can be considered a risk factor for LLNM and LRR.

DISCLOSURES The authors have no conflicts of interest to declare.

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