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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Predictive Factors for Lymph Node Metastasis in Papillary Thyroid Microcarcinoma

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ABSTRACT

Background. Because lymph node (LN) metastasis has been proven to be a predictor for locoregional recurrence (LRR) in papillary thyroid microcarcinoma (PTMC), better knowledge about the predictors for LN metastasis in PTMC is required.

Methods. We retrospectively reviewed 5656 PTMC patients who underwent total thyroidectomy and central neck dissection and/or lateral neck dissection between January 1997 and June 2015.

Results. Male gender (adjusted odds ratio [OR] 2.332), conventional variant (adjusted OR 4.266), tumor size >0.5 cm (adjusted OR 1.753), multiplicity (adjusted OR 1.168), bilaterality (adjusted OR 1.177), and extrathyroidal extension (ETE) (adjusted OR 1.448) were independent predictors for high prevalence of central LN metastasis (CLNM), whereas per 10-year age increment (adjusted OR 0.760) and chronic lymphocytic thyroiditis (adjusted OR 0.791) were independent predictors for low prevalence of CLNM. In addition, male gender (adjusted OR 1.489), tumor size >0.5 cm (adjusted OR 1.295), multiplicity (adjusted OR 1.801), ETE (adjusted OR 1.659), and CLNM (adjusted OR 4.359) were independent predictors for high prevalence of lateral LN metastasis (LLNM), whereas per 10-year age increment (adjusted OR 0.838) was an independent predictor for low prevalence of LLNM. There was a statistically significant difference in LRR with regard to nodal stage ($p < 0.001$).

Conclusions. Meticulous perioperative evaluation of LN metastasis is required for PTMC patients with the above predictors.

According to the World Health Organization, papillary thyroid microcarcinoma (PTMC) is defined as a carcinoma less than 1 cm in size.[1] With the recent widespread use of high-resolution ultrasonography (US), the current increase in the incidence of papillary thyroid carcinoma (PTC) is mainly due to earlier detection of PTMC.[2] The long-term locoregional recurrence (LRR) rate of PTMC has been reported to be up to 8 % with more than 80 % of cases occurring in cervical LN (LN).[3] Because LN metastasis is a proven predictor for LRR in PTMC, the concept of "node beget nodes" was suggested.[3–5]

The prevalence of subclinical central LN metastasis (CLNM) in PTMC has been reported to be 30–65 %.[6–9] Because of difficulties in preoperative detection of CLNM, previous studies have suggested the benefit of prophylactic central neck dissection (CND) in PTMC.[10,11] However, routine prophylactic CND might be associated with significantly higher morbidities, including recurrent laryngeal nerve injury and hypoparathyroidism.[12] Therefore, identification of the predictive factors for CLNM would be important to avoid unnecessary CND in patients with PTMC. Moreover, identification of the predictive factors for lateral LN metastasis (LLNM) could be helpful to determine the necessity for lateral neck dissection (LND). Furthermore, clinicians should consider the possibility of undetected LN metastasis during postoperative period, particularly in PTMC patients who did not underwent neck dissection.

Previous studies of predictive factors for CLNM in PTMC yielded inconsistent data and involved sample sizes of fewer than 1000 cases.[7,8,13–19] Furthermore, studies of the prediction of LLNM in PTMC were based primarily on US findings rather than surgically proven data.[20,21] Therefore, the purpose of this study was to investigate the predictive factors for LN metastasis, including both CLNM and LLNM, using a large group of patients with surgically proven PTMC.

PATIENTS AND METHODS

Patient Selection

This retrospective cohort study was approved by the institutional review board at Samsung Medical Center. Between January 1997 and June 2015, 5656 PTMC patients who underwent total thyroidectomy with CND and/or LND were included for analysis. The patients meeting the following criteria were excluded: age younger than 20 or older than 80 years, a previous history of thyroidectomy, non-PTC carcinomas (follicular/medullary/anaplastic), mixed type PTC, minor variants of PTC except conventional and follicular type, lobectomy cases, total thyroidectomy without CND, tumor size >1 cm, presence of distant metastasis, or follow-up duration less than 6 months (residual tumor or LN detected within 6 months after initial surgery, underwent reoperation within 6 months after initial surgery, or loss to follow-up within 6 months).

Surgical Methods

In general, surgical managements in our institution have been performed following American Thyroid Association Guidelines.[22] Total thyroidectomy was performed when multiplicity, tumor bilaterality, extrathyroidal extension (ETE), or abnormal lymphadenopathy was detected during the preoperative or intraoperative examination. CND was defined as a level VI dissection, which comprised removal of all nodes and fibro-fatty tissue extending vertically from the hyoid bone to the thoracic inlet and laterally from the medial border of the common carotid artery to the midline of the trachea. Therapeutic CND was performed when abnormal lymphadenopathy was detected during the preoperative or intraoperative examination. In the clinically node-negative patients, prophylactic CND was performed based on the surgeon's personal preference at the time of the operation or in the case of advanced primary tumors (T3/T4).[22] LND, including modified radical neck dissection and selective neck dissection, was performed in cases where LLNM was confirmed preoperatively.

Histopathological Examination with Surgical Specimens

Surgical specimens were microscopically examined by two or more experienced pathologists, and the following histopathologic factors were assessed: the cell type of the main lesion, the primary tumor size (measured as the longest diameter of the largest lesion), location, multiplicity, bilaterality, ETE, lymphovascular invasion, margin involvement, LN metastasis, and the underlying conditions of the thyroid, such as chronic lymphocytic thyroiditis (CLT). To distinguish tumor bilaterality from multiplicity, multiplicity was defined as two or more lesions of PTMC in one lobe regardless of the presence of tumor bilaterality. The staging of thyroid cancer was determined in accordance with the American Joint Committee on Cancer.[23]

Postoperative Follow-Up

After the initial surgery, all patients underwent regular follow-up at 6- to 12-month intervals with clinical evaluations, including physical examinations, thyroid US, neck and chest computed tomography, iodine-131 scans, and serum thyroglobulin. Loss to follow-up, withdrawal, and death were censored as of the final date of follow-up. When suspicious lesions were detected, they were confirmed by US-guided aspiration biopsy with or without measurement of washout thyroglobulin level. LRR was defined as the presence of tumor or metastatic LN on cytology from aspiration biopsy or on histopathology from reoperation that developed 6 months after the initial surgery.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 software (IBM Corp, Armonk, NY), and statistically significant differences were defined as those with p values <0.05. Continuous variables were presented as mean ± standard deviation (SD), and categorical variables were presented as the number of cases with percentage (%) and odds ratio (OR). χ^2 test and linear-by-linear association were used for categorical variables and Student's t test for continuous variables. Multivariate analysis using logistic regression analysis was performed on the variables that achieved p values <0.05 in the univariate analysis. The Kaplan–Meier methods and log-rank test were adopted for analysis of time-dependent variables.

RESULTS

Baseline Clinicopathological Characteristics of 5656 PTMC Patients

Of the 5656 patients, 1012 (17.7 %) were men and 4666 (82.3 %) were women. The mean age was 48.0 years, and 3394 patients (60.0 %) were older than 45 years. Conventional open surgery was performed in 5216 (91.8 %) patients, and oncoplastic (endoscopic or robotic) surgery was performed in 462 (8.2 %) patients. Prophylactic CND was performed in 4469 (79.0 %) patients, and therapeutic CND was performed in 1187 (21.0 %) patients. LND was performed in 649 (11.5 %) patients, and all LND was therapeutically performed. Because BRAF mutation analysis was only performed from 2008 in our institution, BRAF status was available for only 1772 patients. BRAF positivity among these patients was 82.6 %. The mean tumor size was 0.6 cm, and 3721 (65.8 %) patients had tumors >0.5 cm. Multiplicity, bilaterality, ETE, and CLT were seen in 1529 (27.0 %), 1538 (27.2 %), 3150 (55.7 %), and 1623 (28.7 %) patients, respectively. Tumor stages were as follows: T1 in 2491 (44.0 %); T3 in 2955 (52.2 %); and T4 in 210 (3.7 %) patients. Nodal stages were N0 in 3014 (53.3 %), N1a in 2124 (37.6 %), and N1b in 518 (9.2 %) patients.

Associations Between Clinicopathological Characteristics and CLNM in PTMC Patients

A total of 5137 patients who underwent total thyroidectomy and CND without LLNM were examined (Tables 1, 2), and 130 patients who underwent LND without LLNM were included. In univariate analysis, male gender ($p < 0.001$), young age ($p < 0.001$), conventional variant ($p < 0.001$), tumor size > 0.5 cm ($p < 0.001$), multiplicity ($p < 0.001$), bilaterality ($p < 0.001$), ETE ($p < 0.001$), and the absence of CLT ($p < 0.001$) were significantly associated with a high prevalence of CLNM. In multivariate analysis, male gender (adjusted odds ratio [OR] = 2.332, $p < 0.001$), conventional variant (adjusted OR 4.266, $p < 0.001$), tumor size >0.5 cm (adjusted OR 1.753, $p < 0.001$), multiplicity (adjusted OR 1.168, $p = 0.026$), bilaterality (adjusted OR 1.177, $p = 0.018$), and ETE (adjusted OR 1.448, $p < 0.001$) were independent predictors for high prevalence of CLNM. However, per 10-year age increment (adjusted OR 0.760, $p < 0.001$) and CLT (adjusted OR 0.791, $p < 0.001$) were independent predictors for low prevalence of CLNM.

TABLE 1 Baseline clinicopathological characteristics of 5656 PTMC patients who underwent total thyroidectomy with CND and/or LND

Clinicopathological characteristics	No. (%)
Male	1002 (17.7)
Age (year)	
Mean ± SD	48.0 ± 10.4
≥45	3394 (60.0)
Surgical approach	
Open	5195 (91.8)
Endoscopic or robotic	461 (8.2)
Neck dissection	
CND	5656 (100)
LND	649 (11.5)
BRAF positivity[a]	1463 (82.6)
PTC variant	
Conventional	5589 (98.8)
Follicular	67 (1.2)
Tumor size (cm)	
Mean ± SD	0.6 ± 0.2
>0.5	3.721 (65.8)
Multiplicity	1529 (27.0)
Bilaterality	1538 (27.2)
ETE	3150 (55.7)
CLT	1623 (28.7)
T stage	
T1	2491 (44.1)
T3	2955 (52.2)
T4	210 (3.7)
N stage	
N0	3014 (53.3)
N1a	2124 (37.6)
N1b	518 (9.1)

PTMC papillary thyroid microcarcinoma, *CND* central neck dissection, *LND* lateral neck dissection, *SD* standard deviation, *ETE* extrathyroidal extension, *CLT* chronic lymphocytic thyroiditis

[a] BRAF mutation analysis was started in 2008 and was performed in 1772 PTMC patients

Associations Between Clinicopathological Characteristics and LLNM in PTMC Patients

A total of 5656 patients who underwent total thyroidectomy with CND and/or LND were examined (Table 3). PTMC patients who did not undergo LND or who underwent LND without LLNM were classified as the absence of LLNM. In univariate analysis, male gender ($p < 0.001$), young age ($p < 0.001$), tumor size >0.5 cm ($p < 0.001$), multiplicity ($p < 0.001$), ETE ($p < 0.001$), and CLNM ($p < 0.001$) were significantly associated with high prevalence of LLNM. However, conventional variant

TABLE 2 Associations between clinicopathological characteristics and CLNM in 5137 PTMC patients who underwent total thyroidectomy and CND without LLNM

	CLNM, no. (%)			MVA[†]	
	Absent	Present	p value	Adjusted OR (95 % CI)	p value
Total	3015 (58.7)	2122 (41.3)	NA	NA	NA
Sex					
Female	2659 (88.2)	1618 (76.2)		Ref	NA
Male	356 (11.8)	504 (23.8)	<0.001	2.332 (1.994–2.726)	<0.001
Age (year)					
Mean ± SD	49.3 ± 9.9	46.7 ± 10.5	<0.001	NA	NA
20–30	70 (2.3)	133 (6.3)		Ref	NA
30–40	497 (16.5)	500 (23.6)			
40–50	1126 (37.3)	768 (36.2)			
50–60	921 (30.5)	490 (23.1)			
60–70	337 (11.2)	206 (9.7)			
70–80	64 (2.1)	25 (1.2)	<0.001	0.760 (0.719–0.803)[‡]	<0.001
PTC variant					
Follicular	49 (1.6)	0 (0.4)	<0.001	Ref	NA
Conventional	2966 (98.4)	2113 (99.6)		4.266 (2.054–8.863)	<0.001
Tumor size (cm)					
Mean ± SD	0.6 ± 0.2	0.7 ± 0.2	<0.001	NA	NA
≤0.5	1253 (41.6)	568 (26.8)		Ref	NA
>0.5	1762 (58.4)	1554 (73.2)	<0.001	1.753 (1.545–1.990)	<0.001
Multiplicity					
Absent	2298 (76.2)	1524 (71.8)		Ref	NA
Present	717 (23.8)	598 (28.2)	<0.001	1.168 (1.019–1.340)	0.026
Bilaterality					
Absent	2260 (75.0)	1494 (70.4)		Ref	NA
Present	755 (25.0)	628 (29.6)	<0.001	1.177 (1.028-1.347)	0.018
ETE					
Absent	1528 (50.7)	830 (39.1)		Ref	NA
Present	1487 (49.3)	1292 (60.9)	<0.001	1.448 (1.284–1.633)	<0.001
CLT					
Absent	2066 (68.5)	1583 (74.6)		Ref	NA
Present	949 (31.5)	539 (25.4)	<0.001	0.791 (0.694–0.901)	<0.001

CLNM central lymph node metastasis, *PTMC* papillary thyroid microcarcinoma, *LLNM* lateral lymph node metastasis, *CND* central neck dissection, *MVA* multivariate analysis, *OR* odds ratio, *CI* confidence interval, *ETE* extrathyroidal extension, *CLT* chronic lymphocytic thyroiditis, *Ref* reference, *NA* not available

PTMC patients who underwent LND without LLNM were included

[†] Variables which achieved $p < 0.05$ in the univariate analysis were included

[‡] Per 10-year age increment

($p = 0.225$), bilaterality ($p = 0.151$), and CLT ($p = 0.156$) were not significantly associated with LLNM. In multivariate analysis, male gender (adjusted OR 1.489, $p < 0.001$), tumor size > 0.5 cm (adjusted OR 1.295, $p = 0.026$), multiplicity (adjusted OR 1.801, $p < 0.001$), ETE (adjusted OR 1.659, $p < 0.001$), and CLNM (adjusted OR 4.359, $p < 0.001$) were independent predictors for high prevalence of LLNM, whereas per 10-year age increment (adjusted OR 0.838, $p < 0.001$) was an independent

predictor for low prevalence of LLNM. Among a total of 519 patients with LLNM, skip metastasis, defined as LLNM with no CLNM, was found in 107 (20.6 %) patients.

Association Between LRR and LN Metastasis in PTMC Patients

The median follow-up time was 61.7 months (range 6.0–213.8). Survival analysis was not performed due to a

TABLE 3 Associations between clinicopathological characteristics and LLNM in 5656 PTMC patients who underwent total thyroidectomy with CND and/or LND

	LLNM, no. (%)			MVA[a]	
	Absent[b]	Present[c]	*p* value	Adjusted OR (95 % CI)	*p* value
Total No.	5137 (90.8)	519 (9.2)	NA	NA	NA
Sex					
Female	4277 (83.3)	377 (72.6)		Ref	NA
Male	860 (16.7)	142 (27.4)	<0.001	1.489 (1.119–1.850)	<0.001
Age (year)					
Mean ± SD	48.2 ± 10.2	45.6 ± 11.4	<0.001	NA	NA
20–30	203 (4.0)	55 (10.6)		Ref	NA
30–40	997 (19.4)	131 (25.2)			
40–50	1894 (36.9)	166 (32.0)			
50–60	1411 (27.5)	112 (21.6)			
60–70	543 (10.6)	48 (9.2)			
70–80	89 (1.7)	7 (1.3)	<0.001	0.838 (0.767-0.914)[d]	<0.00
PTC variant					
Follicular	58 (1.1)	9 (1.7)		NA	NA
Conventional	5079 (98.9)	510 (98.3)	0.225	NA	NA
Tumor size (cm)					
Mean ± SD	0.6 ± 0.2	0.7 ± 0.2	<0.001	NA	NA
≤0.5	1821 (35.4)	114 (22.0)		Ref	NA
>0.5	3316 (64.6)	405 (78.0)	<0.001	1.295 (1.031–1.627)	0.026
Multiplicity					
Absent	3822 (74.4)	305 (58.8)		NA	NA
Present	1315 (25.6)	214 (41.2)	<0.001	1.801 (1.483–2.186)	<0.001
Bilaterality					
Absent	3754 (73.1)	364 (70.1)		NA	NA
Present	1383 (26.9)	155 (29.9)	0.151	NA	NA
ETE					
Absent	2358 (45.9)	148 (28.5)		Ref	NA
Present	2779 (54.1)	371 (71.5)	<0.001	1.659 (1.345-2.046)	<0.001
CLT					
Absent	3649 (71.0)	384 (74.0)		NA	NA
Present	1488 (29.0)	135 (26.0)	0.156	NA	NA
CLNM					
Absent	3015 (58.7)	107 (20.6)		Ref	NA
Present	2122 (41.3)	412 (79.4)	<0.001	4.359 (3.474–5.470)	<0.001

LLNM lateral lymph node metastasis, *PTMC* papillary thyroid microcarcinoma; *CND* central neck dissection, *LND* lateral neck dissection, *MVA* multivariate analysis, *OR* odds ratio, *CI* confidence interval, *ETE* extrathyroidal extension, *CLT* chronic lymphocytic thyroiditis, *CLNM* central lymph node metastasis, *Ref* reference, *NA* not available

[a] Variables which achieved *p* < 0.05 in the univariate analysis were included

[b] PTMC patients who did not undergo LND or who underwent LND without LLNM

[c] PTCM patients who underwent LND with LLNM

[d] Per 10-year age increment

very few number of cause-specific deaths (only five), rather recurrence-free survival was used as the outcome of interest. LRR was observed in 126 patients (2.2 %): 122 (96.8 %) cases occurred in regional LNs and the remaining

4 (3.2 %) cases occurred in the operation bed. From the Kaplan–Meier survival analysis (Fig. 1), the recurrence-free survival rates were 99.5 % at 5 years, 99.1 % at 10 years, and 99.1 % at 15 years in N0 patients; 96.8 % at
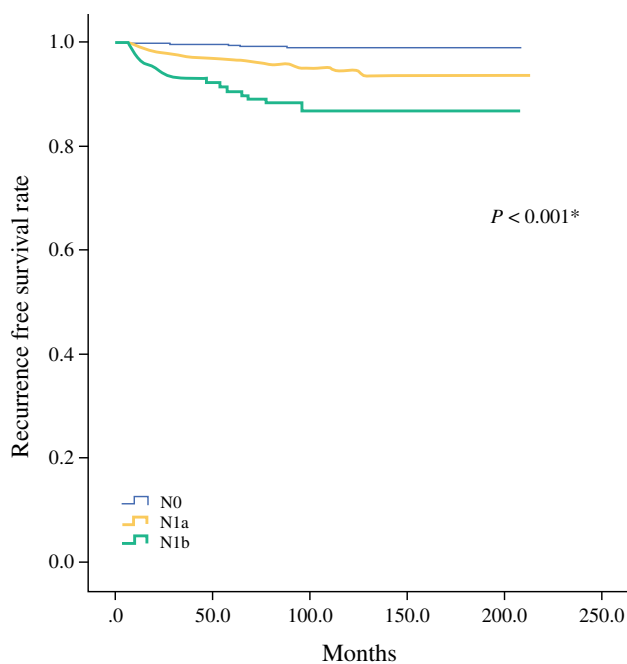
FIG. 1 Unadjusted recurrence-free survival rate for 5656 PTMC patients according to nodal stage. *PTMC* papillary thyroid microcarcinoma. *Calculated using log-rank test

5 years, 94.6 % at 10 years, and 93.6 % at 15 years in N1a patients; and 90.4 % at 5 years, 86.7 % at 10 years, and 86.7 % at 15 years in N1b patients. There was a statistically significant difference in the results of the log-rank test for LRR with regard to nodal stage ($p < 0.001$).

DISCUSSION

We analyzed data for 5656 patients with surgically proven PTMC to investigate the predictive factors for LN metastasis, including both CLNM and LLNM. Because the sensitivity of US for detecting CLNM was <60 % and for detecting LLNM was <70 % in the previous studies, the knowledge of predictive factors of LN metastasis might compensate the sensitivity of US in preoperative period.[24–26] Moreover, the identification of the predictive factors for LN metastasis would be important to avoid unnecessary neck dissection in PTMC patients, particularly who were indicated prophylactic CND.[22] LN metastasis is a proven predictor for recurrence in PTMC; the concept of "node beget nodes" was suggested.[3] Therefore, the assessment of the possibility of LN metastasis during postoperative period also is important, particularly in PTMC patients who did not underwent neck dissection.

To the best of our knowledge, this study is the largest study performed to date to identify predictive factors for LN metastasis in PTMC patients. From multivariate analysis, we showed that male gender, young age, conventional variant, tumor size >0.5 cm, multiplicity, bilaterality, ETE, and the absence of CLT were independent predictors for CLNM (Table 2). Moreover, we found that male gender, young age, tumor size >0.5 cm, multiplicity, ETE, and CLNM were independent predictors for LLNM (Table 3). In previous studies of CLNM, young age, male gender, tumor size >0.5 cm, multiplicity, bilaterality, and ETE were proven as independent predictors for CLNM in PTMC patients.[5,8, 14–19] Previous studies regarding LLNM, reported ETE, CLT, and CLNM as independent predictors in PTMC patients.[20,21] A similarly designed study by Zhang et al. suggested that male gender, age <45 years, tumor size >0.6 cm, ETE, and multiplicity were independent risk factors for CLNM.[13] ETE, multiplicity, bilaterality, and CLNM were independent risk factors for LLNM. Zeng et al. suggested that CLT is an independent predictor for LLNM in PTMC patients; however, other investigators have reported that PTC with the coexistence of CLT is less likely to be associated with ETE, advanced stage, LN metastasis, and recurrence.[21,27–31] In this study, the absence of CLT was an independent predictor for CLNM but was not an indicator for LLNM. Moreover, although a previous study by Lang et al. suggested that significantly more LN metastases were observed in the conventional variant compared with the follicular variant, in our study the conventional variant was a predictor for CLNM, but not for LLNM.[32]

Although American Thyroid Association management guidelines recommend lobectomy in PTMC, more than 5000 PTMC patients underwent total thyroidectomy with CND and/or LND.[33] Advanced tumor stages, T3 or T4, were seen in 3171 (55.9 %) patients in this study (Table 1); this incidence was higher than in previous reports, which showed an incidence of less than 30 % in PTMC patients.[19,34] Moreover, the incidence of BRAF positivity in our study was greater than 80 %; this is similar to other studies in Korea, which is a BRAF-prevalent area.[35–38] A strong association between BRAF mutation and aggressive clinicopathological characteristics of PTC, such as advanced stage, ETE, LN metastasis, and tumor recurrence was previously demonstrated.[39] This finding regarding the incidences of advanced tumor stage and BRAF positivity also could support the geographic bias in this study. Particularly, in this study BRAF mutation status was not included in the multivariate analysis for the following reasons. First, because BRAF mutation analysis was not performed before 2008 in our institution, results were available for only 1772 patients. Second, we previously conducted a study on BRAF mutation and LN metastasis in which we showed that BRAF mutation was an independent predictor for bilaterality but not for CLNM and LLNM.[40] As seen in Table 3, skip metastasis was found in 107 (20.5 %) patients, and this result was consistent with other

studies.[41,42] The finding that nodal stage is a predictor for LRR in PTMC patients (Fig. 1) also confirms previous reports.[3–5]

This study had several limitations. First, there are the inevitable inherent features of a nonrandomized, retrospective cohort study. Therefore, the patient information might not be complete and we cannot rule out the possibility of residual confounding variables of other measured or unmeasured factors. Second, our results may not be applicable to other races or countries, because this study was conducted in a BRAF-prevalent area.[35,36] Third, because LND was performed only for therapeutic purpose in this study, there is the possibility of remaining subclinical LLNM. However, because LND is not generally recommended as a prophylactic procedure, this limitation is inevitable. Nevertheless, this study has several significant strengths. First, we conducted this study on a large group of patients, more than 5000 cases, from a single institution. Second, we used only surgically proven data, rather than US findings.

In conclusion, meticulous perioperative evaluation for CLNM is required for PTMC patients with male gender, young age, conventional variant, tumor size >0.5 cm, multiplicity, bilaterality, ETE, and the absence of CLT. Furthermore, meticulous perioperative evaluation for LLNM is required for PTMC patients with male gender, young age, tumor size >0.5 cm, multiplicity, ETE, and CLNM.

DISCLOSURE The authors have nothing to declare.

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