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Preoperative predictors of lateral neck lymph node metastasis in papillary thyroid microcarcinoma

Zheng Liu, MD[a], Jianyong Lei, MD[b], Yang Liu, MD[a], Yuxia Fan, MD[a], Xiaoming Wang, Master[a], Xiubo Lu, MD[a,*]

Abstract

Lateral lymph node metastasis (LNM) is not uncommon in papillary thyroid microcarcinoma (PTMC). Our present study aimed to investigate the risk factors associated with lateral LNM in PTMC.

We retrospectively collected data pertaining to 366 patients with PTMC who underwent surgery at our center from 2010 to 2015. These patients were divided into the following 2 groups: a lateral LNM-positive group and a lateral LNM-negative group. Clinical and ultrasound data were compared between the 2 groups to determine the risk factors associated with lateral LNM.

Univariate and multivariate analyses indicated that capsule invasion (OR = 3.995, 95% CI, 2.148–7.430) and upper portion location (OR = 4.541, 95% CI, 2.444–8.438) were significant risk factors for lateral LNM of PTMC and that capsule invasion (AUC = 0.666) and upper portion location (AUC = 0.678) could be used to predict lateral LNM of PTMC. Moreover, the patients in lateral LNM positive group exhibited significantly higher rates of tumor recurrence or metastasis than the patients in lateral LNM negative group ($P = 0.027$).

Patients with PTMC located in the upper portion or exhibiting capsule invasion should receive meticulous preoperative evaluations for lateral LNM, prophylactic lateral LND may be considered.

Abbreviations: LND = lymph node dissection, LNM = lymph node metastasis, PTC = papillary thyroid carcinoma, PTMC = papillary thyroid microcarcinoma, ROC = receiver-operating characteristic.

Keywords: lateral neck, lymph node metastasis, papillary thyroid microcarcinoma

1. Introduction

The incidence of papillary thyroid carcinoma (PTC) has increased rapidly in recent years, and PTC is currently the most common malignancy affecting females in Korea[1] and the 3rd most common malignancy affecting individuals in mainland China.[2] Early spread to regional lymph nodes is the characteristic of PTC. It has been reported that lymph node metastases (LNMs) develop in approximately 30% to 80% of PTC patients.[3] Papillary thyroid microcarcinoma (PTMC) is a type of PTC no larger than 10 mm in maximal diameter and is usually indolent and curable with surgical thyroidectomy followed by radioiodine and thyroid stimulating hormone (TSH) suppressive therapy. However, central LNMs have been reported in approximately 3.1% to 82.0% of PTMC patients, and lateral LNMs have been reported in approximately 21.1% of PTMC patients.[4] In particular, lateral LNM may increase the risk of locoregional recurrence and decrease the rate of tumor-free survival among PTC patients. Thus, detection of lateral LNMs during the initial resection operation is very important for reducing reoperation rates and complications of reoperation.[5]

Few studies have attempted to determine the predictors of lateral LNM in PTMC, a topic fraught with controversy, and no studies have attempted to determine the preoperative clinical or ultrasound (US) characteristics predictive of lateral LNM in PTMC. Therefore, our present study aimed to identify the clinical and US predictors of lateral LNM in PTMC, as these factors may guide therapeutic decision-making for surgeons and patients.

2. Patients and methods

We retrospectively collected clinical and pathological data pertaining to 586 patients diagnosed with PTMC who underwent central lymph node dissection (LND) with or without lateral LND in our center from January 2012 to January 2016. The exclusion criteria primarily consisted of medullary or anaplastic thyroid carcinoma, multiple tumor nodes, benign thyroid nodules such as goiter and bilateral LNM, patients loss to follow-up, and cases with important data lost. A total of 366 patients were ultimately included in the study and were evaluated to identify the risk factors predictive of lateral LNM in PTMC. All aspects of the study were approved by the institutional review board of our institution, and all patients provided written informed consent to participate. The 366 patients were divided into the following

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[a] Thyroid Surgery, The First Affiliated Hospital of Zhengzhou University, Zheng Zhou, [b] Thyroid and Parathyroid Center, West China Hospital of Sichuan University, Chengdu, China.

[*] Correspondence: Xiubo Lu, Thyroid Surgery, The First Affiliated Hospital of Zhengzhou University, Zheng Zhou 450052, China (e-mail: henandoctor@163.com).

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2 groups: a lateral LNM-positive group and a lateral LNM-negative group. Patients who underwent additional lateral LND after thyroidectomy were also excluded from this study.

All patients who underwent surgery at our center, including patients with cytological results "suspicious for PTC" and patients positive for BRAF mutations (from November 2015) without a prior histological diagnosis of PTC, were required to undergo fine-needle aspiration (FNA) to confirm a histological diagnosis of PTC. All patients underwent routine presurgical ultrasonography performed by 1 of 4 radiologists with at least 10 years of experience in thyroid imaging. Real-time US-guided and FNA lymph node biopsies were performed on patients with lymph nodes suspicious (central and lateral compartment) for metastasis. Reported characteristics of suspicious LNMs were a diameter greater than 10 mm, a hypoechoic pattern, an irregular cystic appearance, internal calcification, and increased anteroposterior diameter. Thyroglobulin in lymph node washout fluid has been used to detect LNMs in the past 2 years. As recommend in the American Thyroid Association guidelines,[6] prophylactic lateral LND is not recommended in our center, which means only cases with proved lateral LNMs (positive of FNA cytology or thyroglobulin in lymph node washout fluid) would be performed LND.

PTMC characteristics on US imaging, including composition, echogenicity, calcification, margins, maximal diameter, location, and capsule invasion, were noted, and the final 3 characteristics were included in our risk factor analysis. PTMCs were subdivided into the following groups based on their location: upper portion (upper of high plane of isthmus), middle portion (parallel to isthmus), and lower portion (lower of low plane of isthmus), adjacent or nonadjacent to the trachea. Additionally, systemic inflammatory markers that have been reported to be related to LNM,[7] such as the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, were retrospectively reviewed and included in the risk factor analysis. Other clinicopathologic characteristics potentially related to LNM, including patient age, gender, body mass index, autoimmune thyroid disease history, goiter history, TSH levels, and tumor stage, were also investigated.

Continuous data were expressed as means ± SD, and differences in continuous data were analyzed using the Mann–Whitney *U* test. The χ^2 test or Fisher exact test was used to compare categorical variables, and *t* tests were used to compare continuous variables. Univariate analysis was performed to identify LNM risk factors following adjustment for various established clinicopathological factors, and factors found to be significant in the univariate analysis were included in the multivariate logistic regression analysis, which was performed to identify independent factors associated with lateral LNM. Receiver-operating characteristic (ROC) curves were constructed based on the results of multiple logistic regression analysis and were used to identify the data points with the highest sensitivity and lowest false-negative rate. *P*-values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS 17.0 (SPSS, Inc., Chicago, IL).

3. Results

3.1. Comparisons of clinicopathological and US characteristics between patients with and without lateral LNMs

Clinicopathological and US characteristics were compared between patients with and without LMNs, as presented in Table 1. The patients in lateral LNM positive group were more likely to exhibit capsule invasion (67.7% vs 34.5%, $P < 0.001$) and to present with advanced-stage disease than the patients in lateral LNM negative group (62.9% vs 43.1%), indicating that PTCs with lateral LMNs are more likely to have invaded the thyroid capsule and the surrounding tissues than PTCs without lateral LMNs. Additionally, the patients in lateral LNM positive group were more likely to have PTMCs located in the upper portion than the patients in lateral LNM negative group (42 [67.7%] in lateral LNM positive group and 98 [32.2%] in lateral LNM negative group, presented $P < 0.001$).

Table 1

Comparisons of clinicopathological and US characteristics between the 2 groups of patients with PTMC.

Variable	Positive or negative for lateral LNM: lateral LNM positive group (n = 62)	lateral LNM negative group (n = 304)	*P*
Mean age at diagnosis, years	41.0 ± 13.8	41.2 ± 13.7	0.919
≤45	37	198	0.415
>45	25	106	
Gender (M/F)	18/44	83/221	0.782
BMI, kg/m^2	23.0 ± 3.0	23.0 ± 3.4	0.869
<24	39	203	0.558
≥24	23	101	
Hashimoto's thyroiditis (yes/no)	41/21	225/79	0.205
Graves' disease (yes/no)	2/60	6/298	0.539
Nodular goiters (yes/no)	39/23	195/109	0.853
NLR (≤2/>2)	41/21	195/109	0.766
PLR (≤200/>200)	60/2	295/9	0.911
TSH level (≤4.2/>4.2 mU/L)	45/17	246/58	0.139
Multifocality (yes/no)	7/55	54/250	0.109
Bilaterality (yes/no)	3/59	51/253	0.206
Capsule invasion (yes/no)	42/20	105/199	<0.001*
Extrathyroid extension (yes/no)	20/42	69/235	0.282
Total tumor size	7.4 ± 1.9	8.3 ± 2.4	0.105
≤10 mm	56	256	0.356
>10 mm	6	48	
Primary tumor size	7.3 ± 1.6	7.4 ± 1.7	0.488
≤5 mm	11	52	0.573
>5 mm	51	252	
Tumor extension (T1/T2/T3/T4)	24/0/27/12	173/0/109/22	0.001*
Tumor location (upper/middle/lower)	42/10/10	98/110/95	<0.001*
Calcification			0.786
Undetectable	12	71	
Microcalcification	46	206	
Macrocalcification	4	27	
Echogenicity			0.587
Hyperechogenicity	10	58	
Hypoechogenicity	52	246	

BMI = body mass index, F = female, LNM = lymph node metastasis, M = male, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, PTMC = papillary thyroid microcarcinoma, TSH = thyroid stimulating hormone, US = ultrasound.

3.2. Multivariate analysis of lateral LNMs

Multivariate logistic regression analysis including the significant predictors identified via univariate analysis was performed to determine the independent factors associated with lateral LNM following adjustment for various other factors. As shown in Table 2, we observed significant associations between lateral LNM and the following tumor characteristics: PTMCs exhibiting

Table 2

Multivariate analyses of the association between lateral LNM and PTMC.

Variables	Odds ratio	95% CI	*P*
Capsule invasion (yes/no)	3.981	2.242–7.520	<0.001*
Tumor extension (T1 + T2/T3 + T4)	0.0512	0.982–3.431	0.059
Tumor location (upper/middle + lower)	4.498	2.326–8.549	<0.001*
TSH level (≤4.2/>4.2 mU/L)	1.328	0.882–1.682	0.682
Multifocality (yes/no)	1.582	1.211–2.162	0.218
Primary tumor size (≤5 mm/>5 mm)	1.272	1.101–1.532	0.326

CI = confidence interval, LNM = lymph node metastasis, PTMC = papillary thyroid microcarcinoma, TSH = thyroid stimulating hormone.

capsule invasion, which had an OR of 3.981 (95% CI, 2.242–7.520) for lateral LNM, and for PTMCs located in the upper portion, which had an OR of 4.498 (95% CI, 2.326–8.549) for lateral LNM (all $P < 0.001$). Advanced tumor stage was another potential predictor of lateral LNM; however, the difference in tumor stage, TSH level, and multifocality between patients with and without LMN did not reach statistical significance ($P > 0.05$).

3.3. ROC curve analysis of lateral LNM predictors

Multiple logistic regression analysis demonstrated that capsule invasion, advanced tumor extension, and upper portion tumor location were associated with lateral LNM in patients with PTMC and could therefore be used as predictors of lateral LNM of PTMC. The high sensitivities and low false-negative rates (1-specificity) associated with these parameters were identified via ROC curve analysis, as depicted in Fig. 1.

3.4. Lateral LNM patterns

From the 62 PTMC patients with lateral LNM, a mean of 17.4 ± 8.1 lateral neck lymph nodes were harvested, and 6.1 ± 2.9 of these nodes contained metastases. The distribution of lateral LNMs is presented in Table 3. The most common distribution pattern was lateral LNMs at 3 levels (27 patients, 43.5%). The 2nd most common distribution of metastases was lateral LNMs at 2 levels (24 patients, 38.7%), especially levels II and III or levels III and IV. Few patients (8, 12.9%) showed lateral LNMs at a single level (II, III, or IV), and 3 patients (4.8%) had lateral LNMs at 4 levels (II + III + IV + V). Fifty-four patients (87.1%) exhibited level III LNMs, 40 patients (64.5%) exhibited level IV LNMs, 34 patients (54.8%) exhibited level II LNMs, and 19 patients (30.6%) exhibited level V LNMs.

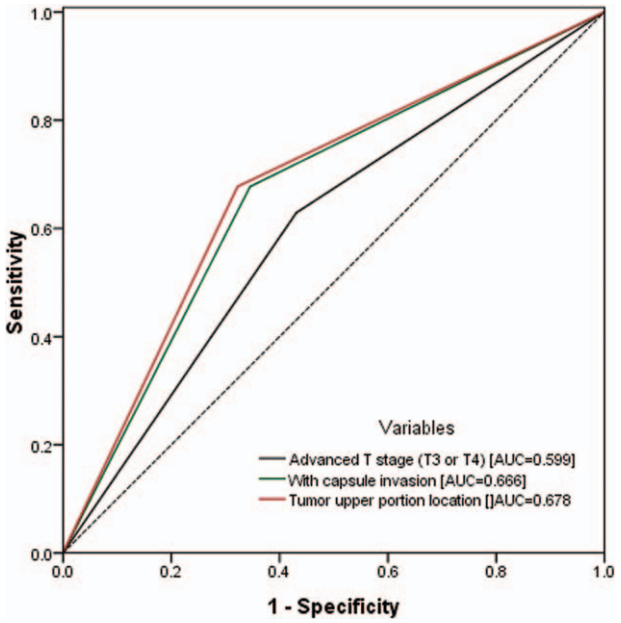

Figure 1. ROC curve comparasion the sensitivities and false-negative rates of capsule invasion, advanced tumor extension, and upper portion tumor location on predicting lateral LNM in patients with PTMC. LNM = lymph node metastasis, PTMC = papillary thyroid microcarcinoma, ROC = receiver-operating characteristic.

3.5. Postoperative PTC recurrence and metastasis

Eight patients in lateral LNM positive group presented with PTC recurrence or metastasis within a mean of 22.4 months (8–35 months) of follow-up, 2 of which exhibited lateral lymph node recurrence, 5 of which exhibited lung metastasis, and 1 of which exhibited bone metastasis. Fifteen patients in lateral LNM negative group were diagnosed with PTC recurrence or metastasis within a mean of 15.1 months (3–58 months) of follow-up: 6 patients with lateral LNM, 6 patients with lung metastasis, 2 patients with bone metastasis, and 1 patient with lung and bone metastasis. The frequency of long-term PTC recurrence or metastasis was significantly higher in lateral LNM positive group than in lateral LNM negative group, as demonstrated in Fig. 2 ($P = 0.027$).

4. Discussion

This study is among the largest case series reporting on the risk factors for LNM in PTMC. Our results indicate that patients with

Table 3

Distribution of metastases in lateral neck lymph nodes from 62 papillary thyroid microcarcinoma (PTMC) patients.

Distribution (II–V)	Number of patients
Single level (II/III/IV)	2/3/3
Two levels	24
II + III	8
III + IV	12
II + V	2
III + V	1
IV + V	1
Three levels	27
II + III + IV	13
II + III + V	6
III + IV + V	8
Four levels	
II + III + IV + V	3

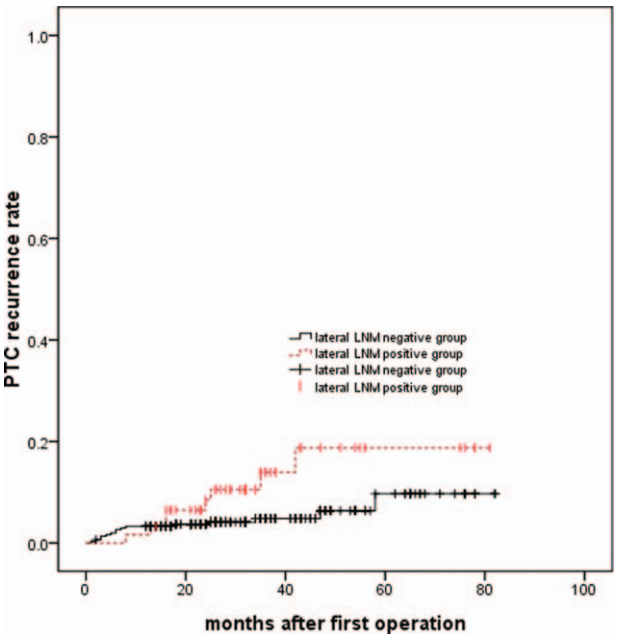

Figure 2. Long-term PTC recurrence or metastasis was significantly higher in lateral LNM positive group than in lateral LNM negative group ($P < 0.05$). LNM = lymph node metastasis, PTC = papillary thyroid carcinomas.

PTMC located in the upper portion or exhibiting capsule invasion are at risk for lateral LNM. In such cases, lateral LNM should therefore be evaluated carefully, especially in patients with PTMC exhibiting both risk factors simultaneously. Our study has also demonstrated that the above factors are significant predictors of lateral LNM, as demonstrated by ROC curve analysis. Finally, our results demonstrated that lateral LNMs may predispose patients to local tumor recurrence or distant metastasis.

Developments in US technology have enabled the detection of a wider range of impalpable small-sized PTMCs (with diameters no larger than 10 mm). However, much controversy remains regarding the extent of surgical resection and LND that is necessary to treat PTMCs. Some investigators have argued that 3.7% to 44.5% of PTMC cases exhibit lateral LNM[8,9] and that LNM increases the risk of disease recurrence.[10] In contrast, another study reported that the prognoses of PTMC patients were not affected by the surgical extent,[11] and those findings were supported by the American Thyroid Association, whose recent guidelines recommend reducing the surgical extent of primary tumor resection LND in cases of PTMC.[6] However, modified radical (II–V regions, not include sternocleidomastoid, jugular vein, and accessory nerve) lateral LND should be recommended for patients in whom lateral LNM has been confirmed preoperatively. Prophylactic lateral LND is not recommended in our center, however, for cases with proved lateral LNMs (positive of FNA cytology or thyroglobulin in lymph node washout fluid), our center recommends performing LNDs involving levels II to V during the initial operation in these patients, as adhesions from the initial surgery would make reoperation difficult. Furthermore, additional operations increase the risk of complications such as spinal accessory nerve damage. Thus, adequate modified radical LND should be performed on patients with lateral LNM as confirmed preoperatively.

Preoperative US is the most common method of detecting the absence of cervical LNM; however, there are still limitations associated with diagnosing LNM via US, which exhibits a sensitivity of only 65% to 80.3% and a specificity of 72% to 84.8% for the detection of lateral LNMs.[12,13] US is also limited with respect to the evaluation of deep lymph nodes, such as the retropharyngeal and mediastinal nodes.[14,15] Due to the high incidence of postoperative complications, such as pain, bleeding, cervical chylous fistulae, and nerve damage, prophylactic lateral LND is not recommended routinely. However, accurate preoperative prediction of lateral LNM may be helpful in managing patients with PTMC and may facilitate more careful selection of patients for lateral LND.

In our study, 62 of 366 (16.9%) PTMC cases exhibited lateral LNMs, and this incidence was significantly lower than that reported by other studies (30%–55%)[8,16–19] but was higher than that reported by Kwak et al (3.7%).[8] Thus, prophylactic lateral LND is not recommended at our center. Comparisons of the clinicopathologic and US characteristics of patients with PTMC demonstrated that advanced tumor stage, capsule invasion, and upper portion location were significantly associated with lateral LNM. However, multivariate analyses indicated that only capsule invasion and upper portion location were significant risk factors for lateral LNM in PTMC patients. The main reason why an upper portion location may increase the risk of lateral LNM may be that PTMC cells from the upper region are more likely to be transported to the lateral lymph nodes via the lymphatic flow along the superior thyroid artery.[19,20] In our present study, all of the capsular invasion and tumor location was radiographic finding. Therefore, detection of PTMC located in the upper portion exhibiting capsule invasion may be a useful diagnostic marker of LNM preoperatively.

Tumor size may be an important prognostic factor related to lateral LNM. Lee et al[21] demonstrated that PTMCs with tumor sizes >7 mm were more frequently associated with LNM than PTMCs with tumor sizes <7 mm, and other studies have demonstrated that PTMCs with tumor sizes >5 mm were more likely to lead to LNM than PTMCs with tumor sizes <5 mm.[22] However, the present study did not identify a tumor size cutoff value that may be used to predict LNM, similar to the results of previous studies.[19] Patients with Hashimoto thyroiditis are believed to be at increased risk of developing PTC. The combination of Hashimoto thyroiditis with PTC or PTMC has been negatively associated with central LNM.[23] However, other studies reported that underlying Hashimoto thyroiditis was significantly positively associated with lateral LNM.[19,24] In our study, we found no difference in the frequency of lateral LNM between patients with and without Hashimoto thyroiditis. Although microcalcifications were associated with US-diagnosed lateral LNM, the presence or absence of calcifications in PTMC showed no association with lateral LNM,[14] and those findings were consistent with the report by Zeng et al.[19]

Lateral LNM is most commonly observed at level III (87.1%), followed by level IV (64.5%), level II, and level V. Formation of lateral LNMs at 3 levels was the most commonly observed pattern, which was detected in 27 patients (43.5%). The 2nd most common LNM distribution pattern was 2 levels, which was observed in 24 patients (38.7%) in this study. These findings indicate that multilevel lateral LNM was common in PTMCs, similarly to previous studies.[8,25] It has been reported that the risk of tumor recurrence is 6-fold higher in patients with LNM, over 80% of whom exhibit distant metastasis,[15,26] than in patients without LNM. In particular, patients with lateral LNM are more likely to develop tumor recurrence.[27] Those results are consistent with our finding of a difference in tumor recurrence between lateral LNM positive group and B ($P = 0.027$).

There were several limitations to this study. First, prophylactic lateral LND was not performed on the patients in lateral LNM negative group, in whom subclinical LNM may have been present, potentially resulting in an underestimation of the incidence of lateral LNM. However, given the complications and ethical issues associated with prophylactic lateral LND, this procedure cannot be recommended for every case of PTMC. Second, this study may also be limited by its retrospective design, the limited number of PTMC cases, and analysis of a single center. Thus, multicenter and large cohorts study should be performed in the future to identify the risk factors associated with lateral LNM in patients with PTMC.

In conclusion, lateral LNM in cases of PTMC was statistically significantly associated with an upper portion tumor location and with capsule invasion, prophylactic lateral LND may be considered. Preoperative evaluations should be meticulously performed on patients presenting with these features.

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