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

Zheng Liu, MD, Jianyong Lei, MD, Yang Liu, MD, Yuxia Fan, MD, Xiaoming Wang, Master, Xiubo Lu, MD.

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 10mm 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 recurrence 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
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 LNsMs were a diameter greater than 10 mm, a hypoechoic pattern, an irregular cystic appearance, internal calcification, and increased anteroposterior diameter. Thryoglobulin in lymph node washout fluid has been used to detect LNsMs 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 LNsMs (positive of FNA cytology or thryoglobulin 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 thyroid capsule and the surrounding tissues), and lower portion (lower of low plane of isthmus), which means only cases with proved lateral LNsMs (positive of FNA cytology or thryoglobulin in lymph node washout fluid) would be performed LND.

Continuous data were expressed as means ± SD, and differences in continuous data were analyzed using the Mann–Whitney U test. The χ² 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 other factors. As shown in Table 1, we observed significant predictors identified via univariate analysis were 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 malignancy, margins, maximal diameter, location, TSH levels, and tumor stage, were also investigated.

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3. Results

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

Clinicopathological and US characteristics were compared between patients with and without LNsMs, as presented in

| Table 1 | Comparisons of clinicopathological and US characteristics between the 2 groups of patients with PTMC. |
|----------------------------------------|---------------------------------|
| Variable | 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 |
| Gender | | | |
| Male | 37 | 198 | 0.415 |
| Female | 25 | 106 | |
| BMI, kg/m² | 23.0±3.0 | 23.0±3.4 | 0.869 |
| <24 | 29 | 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 goiter (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 |
| Capsule invasion (yes/no) | | | |
| ≥5 mm | 6 | 48 | |
| <5 mm | 51 | 252 | |
| Tumor location | | | |
| T1/T2/T3/T4 | 24/0/27/12 | 173/0/109/22 | 0.001* |
| Calcification | | | |
| Undetectable | 12 | 71 | |
| Microcalcification | 46 | 206 | |
| Macrocalcification | 4 | 27 | |
| Echogenicity | | | |
| Hypochoicogenicity | 10 | 58 | |
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B = 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.
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 $17.4 \pm 8.1$ lateral neck lymph nodes were harvested, and $6.1 \pm 2.9$ of these nodes contained metastases. The distribution of lateral LNM is presented in Table 3. The most common distribution pattern was lateral LNM at 3 levels (27 patients, 43.5%). The 2nd most common distribution of metastases was lateral LNM at 2 levels (24 patients, 38.7%), especially levels II and III or levels III and IV. Few patients (8, 12.9%) showed lateral LNM at a single level (II, III, or IV), and 3 patients (4.8%) had lateral LNM at 4 levels (II+III+IV+V). Fifty-four patients (87.1%) exhibited level III LNM, 40 patients (64.5%) exhibited level IV LNM, 34 patients (54.8%) exhibited level II LNM, and 19 patients (30.6%) exhibited level V LNM.

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 ($P = 0.027$).

### 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      | 1.101–1.522  | 0.326 |

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

### 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 (III/V)         | 2/3/3              |
| Two levels                   | 24                 |
| II + III                     | 8                  |
| III + N                     | 12                 |
| II + V                      | 2                  |
| III + V                     | 1                  |
| N + V                       | 1                  |
| Three levels                 | 27                 |
| II + III + IV               | 13                 |
| II + III + V                | 6                  |
| III + N + V                 | 8                  |
| Four levels                  |                    |
| II + III + IV + V           | 3                  |
another study reported that the prognoses of PTMC patients modiﬁed preoperatively. 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. 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. 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. 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. 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. 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. However, other studies reported that underlying Hashimoto thyroiditis was signiﬁcantly positively associated with lateral LNM. 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, and those ﬁndings were consistent with the report by Zeng et al.

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 LNs is the most commonly observed distribution pattern was 2 levels, which was observed in 24 patients (38.7%). 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. It has been reported that the risk of tumor recurrence is 6-fold higher in patients with LNM, over 50% of whom exhibit distant metastasis, than in patients without LNM. In particular, patients with lateral LNM are more likely to develop tumor recurrence. 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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