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RESEARCH ARTICLE

Predicting the factors of lateral lymph node metastasis in papillary microcarcinoma of the thyroid in eastern China

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Abstract

Introduction Lateral lymph node metastasis is common in papillary thyroid microcarcinoma (PTMC). The present study evaluated the clinicopathologic characteristics and ultrasonographic (US) findings in predicting lateral LNM from PTMC in eastern China.

Materials and methods A total of 176 patients with confirmed PTMC by final histological examination who underwent central lymph node dissection (LND) and lateral LND were enrolled in our study. The clinicopathological and US data from the cases were analyzed retrospectively to determine the independent predictive factors for lateral LNM. Then, a scoring system was developed on the basis of independent factors. The sum of the points for individuals was evaluated for the value in predicting lateral LNM.

Results Central LNM, underlying Hashimoto's thyroiditis, upper pole location, no well-defined margin and presence of calcifications were independent predictive factors for lateral LNM on multivariate analysis. Clinicopathological and US index points were statistically significant, with ≤2 favoring lateral LNM negativity with a sensitivity of 83.3 %, positive predictive value of 89.6 % and negative predictive value of 72.9 %.

Conclusions When the evaluation for lateral lymph nodes from a preoperative approach is inadequate or not obvious, our scoring system for prediction of lateral LNM can be another choice. Patients with clinicopathological and US index points ≤2 could be considered as lateral LNM negative, so more diagnostic approach is recommended for patients with clinicopathological and US index points >2.

Keywords Thyroid neoplasms · Papillary thyroid microcarcinoma · Ultrasonographic · Lateral lymph node metastasis

Abbreviations

LNM	Lymph node metastasis
PTMC	Papillary thyroid microcarcinoma
PTC	Papillary thyroid carcinoma
ROC curves	Receiver-operating characteristic curves
US	Ultrasonographic
FNAC	Fine-needle aspiration cytology
LND	Lymph node dissection

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Introduction

Papillary thyroid microcarcinoma (PTMC) is a papillary thyroid carcinoma (PTC) primary tumor that is ≤10 mm in diameter, as defined by the World Health Organization (WHO) [1]. In the past, many patients with PTMC were found from specimens of thyroid removed for benign diseases, such as Graves' disease, follicular adenoma, and multinodular goiter. PTMC was also found commonly on autopsy of patients who had died of non-thyroid-related diseases [2, 3]. The number of patients with PTMC has been increasing due to the use of ultrasonography (US) and US-guided fine-needle aspiration cytology (FNAC) for diagnosis preoperatively in recent years in eastern China [4]. PTMC has an excellent prognosis after surgical treatment, but a subgroup of PTMC is aggressive and shows easier recurrence or distant metastases in patients with lymph node metastasis [5, 6]. The approach for evaluating the status of lymph nodes preoperatively has been extensively investigated. Recent reports support that central lymph node dissection (LND) should be routinely performed [7, 8]. So, our study focused on the status of the lateral compartment. We investigated the relationship between lateral LNM and the clinicopathological, US characteristics to find the risk factors for lateral LNM. In addition, we develop a scoring system on the basis of clinicopathological and US characteristics. Then, we evaluate the value of the scoring system in differentiating between patients with and without lateral LNM.

Materials and methods

Patients

Between January 2005 and December 2010, 534 patients with PTMC underwent central LND with or without lateral LND at our hospital. All the patients had undergone US preoperatively and had confirmed PTMC by final histological examination. For selection of cases, the exclusion criterion in this study included patients who had a history of thyroid or neck surgery for nonthyroidal head and neck cancers; US-detectable lateral LNM was not considered an exclusion criterion. Finally, 176 patients who underwent both central and lateral LND were retrospectively analyzed to evaluate risk factors in predicting lateral LNM. All the patients were from eastern China (most of the patients were from Wenzhou City) and received primary treatment in our hospital. Table 1 lists the clinicopathologic data of all patients.

Clinicopathological and US features

Through the retrospective review of clinical data and pathologic reports, age at diagnosis, sex, pathologic tumor size, the status of central lymph nodes, and underlying Hashimoto's thyroiditis were recorded. Central LNM was identified as present at one or more metastatic lymph nodes confirmed by frozen biopsy with 100 % sensitivity and 98.8 % specificity. Hashimoto's thyroiditis was defined by serological examination or frozen biopsy with 100 % sensitivity and 99.3 % specificity. The status of lateral lymph nodes was confirmed by a final histological examination. US was performed with Acuson Sequoia and 128XP sonographic scanners (Siemens Medical Solutions, Mountain View, CA) equipped with commercially available 8- to 13-MHz linear probes. US features of patients were recorded according to composition, echogenicity, calcifications, margin, location of tumor, width/length, and contact of >25 % with the adjacent capsule. When multiple PTMC were found in the specimen, the largest tumor or the most suspicious dominant nodule was analyzed.

Table 1 Patient clinicopathological and US characteristics of 176 patients

Characteristics	Value
Total number	176
Age	
Mean age at diagnosis (years) (range)	44.9 ± 10.8 (17–76)
<45 years	91 (51.7 %)
≥45 years	85 (48.3 %)
Sex	
Female	131 (74.4 %)
Male	45 (25.6 %)
Pathologic tumor size (mm) (range)	6.3 ± 2.4 (2–10)
Tumor location	
Upper	61 (34.7 %)
Middle	71 (40.3 %)
Lower	40 (22.7 %)
Isthmus	4 (2.3 %)
Central lymph node metastasis	
Yes	91 (51.7 %)
No	85 (48.3 %)
Lateral lymph node metastasis	
Yes	62 (35.2 %)
No	114 (64.8 %)

Data are expressed as mean ± standard deviation and *n* (%)

Statistical analysis

We divided the analysis into two groups: lateral LNM positive (Group I) and lateral LNM negative (Group II). Statistical analysis was performed between these two groups. We used χ^2 test or Fisher's exact test for categorical data. Independent two-sample *t* test was used to compare continuous variables. Nonparametric data with continuous variables were compared by the Mann–Whitney *U* test. Multivariate logistic regression analysis was performed to assess independent associations of lateral LNM with all factors found to be statistically significant by univariate analysis with adjustment for various established clinicopathological factors. Results were presented as odds ratio (OR) with 95 % confidence interval (CI) and *P* value.

$P < 0.05$ was considered to be statistically significant. According to multiple logistic regression analysis, features which were independent factors were given different points for developing a score system. Then using receiver-operating characteristic curves (ROC curves), based on the multiple logistic regression analysis, we identified the best point with high sensitivity and low false-negative rate (1-specificity).

Results

Clinicopathological and US features between patients with and without lateral LNM

Clinicopathological and US differences between Group I and Group II are compared in Table 2. Central LNM was found in 91 (51.7 %) patients and lateral LNM in 62 (35.2 %) of the 176 patients. Skip metastasis, defined as having lateral LNM without central LNM, was found in only 15 (8.5 %) patients. CNM was statistically significant with lateral LNM ($P < 0.001$). Incidence of lateral LNM was greater in patients with Hashimoto's thyroiditis ($P = 0.027$) and microcalcifications ($P < 0.001$). No well-defined margin was statistically related to lateral LNM ($P = 0.018$). Upper pole location and contact of >25 % with the adjacent capsule on US were significantly associated with lateral LNM ($P < 0.001$ and $P = 0.010$, respectively).

Multivariate analysis

Factors found to be statistically significant on univariate analysis were analyzed to assess independent association of lateral LNM using multivariate logistic regression. Previously, age at diagnosis, sex, and tumor size had been proven to be associated with clinical outcomes in thyroid cancer patients [9–11]. After adjusting for the established clinicopathological prognostic factors and the remaining statistically significant predictive factors, the associations between central LNM, underlying Hashimoto's thyroiditis, upper pole location, no well-defined margin, and the presence of calcifications with the presence of lateral LNM were highly significant as in Table 3.

Clinicopathological and US index points to distinguish between patients without and with lateral LNM

According to multiple logistic regression analysis, central LNM, underlying Hashimoto's thyroiditis, upper pole location, no well-defined margin, and presence of calcifications were statistically significantly associated with lateral LNM, and the estimate and point of each characteristic are shown in Table 4. The sum of the points was evaluated

Table 2 Clinicopathological and US characteristics according to lateral lymph node metastasis

Characteristics	Status of metastatic lateral lymph node		P value
	Group I	Group II	
Total number	62	114	
Age at diagnosis			
Mean age at diagnosis (year)[a]	44.2 ± 11.6	45.2 ± 10.4	0.552
<45 years	36 (58.1)	55 (48.2)	0.213
≥45 years	26 (41.9)	59 (51.8)	
Sex			0.063
Female	41 (66.1)	90 (78.9)	
Male	21 (33.9)	24 (21.1)	
Pathologic tumor size (mm)[b]	6.8 ± 2.3	6.1 ± 2.5	0.056
≤5	15 (24.2)	43 (37.7)	0.068
>5	47 (75.8)	71 (62.3)	
≤7	37 (59.7)	75 (65.8)	0.421
>7	25 (40.3)	39 (34.2)	
Central lymph node metastasis			<0.001*
Yes	47 (75.8)	44 (38.6)	
No	15 (24.2)	70 (61.4)	
Underlying Hashimoto's thyroiditis			0.027*
Yes	15 (24.2)	13 (11.4)	
No	47 (75.8)	101 (88.6)	
Composition			0.431
Solid	50 (81)	86 (75)	
Cystic or mixed	12 (19)	28 (25)	
Echogenicity			0.737
Hyperechogenicity or isoechoic	17 (27.4)	34 (29.8)	
Hypoechogenicity	45 (72.6)	80 (70.2)	
Calcification			<0.001*
Absence	12 (19.4)	72 (63.2)	
Microcalcification	43 (69.4)	28 (24.6)	
Other calcification	7 (11.3)	14 (12.2)	
Margin			0.018*
Well-defined margin	40 (64.5)	92 (80.7)	
No well-defined margin	22 (35.5)	22 (19.3)	
Tumor location			<0.001*
Upper	34 (54.8)	27 (23.7)	
Middle/lower/isthmus	28 (45.2)	87 (76.3)	
Shape			0.289
Taller than wide	42 (67.7)	68 (59.6)	
Wider than tall	20 (32.3)	46 (40.4)	
Contact of >25 % with the adjacent capsule			0.010*
Yes	27 (43.5)	23 (20.2)	
No	35 (56.5)	91 (79.8)	

Data are expressed as mean ± standard deviation and n (%). Group I: lateral lymph node metastasis positive. Group II: lateral lymph node metastasis negative

* Statistically significant ($P < 0.05$)

[a] P value using independent two-sample t test

[b] P value using the Mann–Whitney U-test; other P value using χ^2 test or Fisher's exact test

Table 3 Multivariate analysis of association of lateral lymph node metastasis with clinicopathological and US characteristics

Characteristic	OR	95 % CI	*P* value
Central lymph node metastasis	7.530	2.864–19.802	<0.001
Underlying Hashimoto's thyroiditis	5.366	1.718–16.758	0.004
Upper pole location	6.006	2.325–15.513	<0.001
Contact of >25 % with the adjacent capsule	2.368	0.951–5.901	0.064
No well-defined margin	4.580	1.723–12.180	0.002
Presence of calcification	6.871	2,778–16.998	<0.001

OR odds ratio, *95 % CI* 95 % confidence interval

for distinguishing between patients without and with lateral LNM. Using ROC curves, we identified the best point with high sensitivity and low false-negative rate (1-Specificity) (Fig. 1).

Mean clinicopathological and US index points were 3.40 ± 1.05 in Group I and 1.54 ± 1.14 in Group II, which was statistically significant ($P < 0.001$). Clinicopathological and US index points ≤2 were found to be best for distinguishing between patients without and with lateral LNM, the sensitivity and specificity were 83.3 and 82.3 %, respectively, and the positive and negative predictive values were 89.6 and 72.9 % (Table 5).

Discussion

The incidence of PTMC in eastern China is greater than in other areas in china. In recent years, the prevalence of PTMC has shown an increasing trend owing to the diagnostic scrutiny by US and US-guided FANC in eastern China [4]. Lymph node metastasis, considered as a risk factor for poor clinical outcome [12, 13], is common in patients with PTMC. Therefore, the preoperative detection

Table 4 Clinicopathological and US index points

Feature	Characteristic	Points
Central lymph node metastasis	Yes	1
	No	0
Underlying Hashimoto's thyroiditis	Yes	1
	No	0
No well-defined margin	Yes	1
	No	0
Tumor location	Upper	1
	Lower/middle/isthmus	0
Calcifications	Microcalcifications	2
	Other calcifications	1
	Absent	0

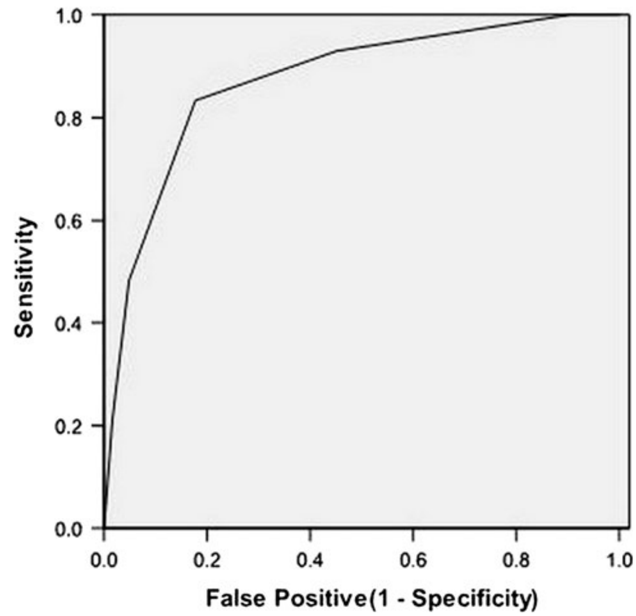

Fig. 1 Receiver-operatering characteristic (ROC) curve for lateral lymph node metastasis. Index points ≤2 were found to be best for distinguishing between patients without and with lateral LNM. The sensitivity and specificity were 83.3 and 82.3 %, respectively, and the positive predictive value and negative predictive value were 89.6 and 72.9 %

Table 5 Sensitivity and specificity of clinicopathological and US index points

	Index points ≤2 for lateral lymph node metastasis negative	Index points >2 for lateral lymph node metastasis positive
Sensitivity (%)	83.3	82.3
Specificity (%)	82.3	83.3
Positive predictive value (%)	89.6	72.9
Negative predictive value (%)	72.9	89.6

of lateral LNM is important for reducing the recurrence when central LND is routinely performed during thyroid cancer surgery. However, there have been few reports on the role of preoperative and intraopertive information of clinicopathological and US findings in evaluating the status of lateral neck in eastern China. Our goal in this study was to find the preoperative and intraopertive predicting factors for lateral LNM, which was helpful in planning appropriate surgical treatment for each patient in eastern China.

The incidence of lateral LNM in patients with PTMC was about 30–55 % [14–17]. The incidence found in our study was 35.2 % ($n = 62$), which is compatible with previous studies. Results of statistical analyses performed for Group I and Group II in our study showed that clinicopathological (central LNM and underlying Hashimoto's thyroiditis) and US features (upper pole location, no well-defined margin, and presence of calcifications) were independent predictors for lateral LNM on multivariate analysis. Kwak et al. showed that US features (upper pole location, contact of 25 % with the adjacent capsule, and presence of calcifications) and pathologic features (CNM) were considered as predicting factors for lateral LNM [17]. Kwak et al. enrolled patients with no metastatic disease, as confirmed by US, and so the actual number of patients who underwent both central and lateral LND was 64 [17]. In our study, we only enrolled patients who had both central and lateral LND ($n = 176$), and the status of lateral lymph nodes was determined by final histological examination.

Tumor size is an important prognostic feature of lateral LNM [18]. Lee et al. [19] demonstrated that PTMC with tumor size >7 mm was frequently associated with central LNM. However, Kwak et al. [17] showed that tumor size was not significantly associated with lateral LNM in patients with PTMC. In our study, we found no difference in tumor size between patients with and without lateral LNM. Patients with Hashimoto's thyroiditis are believed to be at higher risk of having thyroid carcinoma compared to patients without it [21, 22]. Coexisting Hashimoto's thyroiditis in patients with papillary thyroid carcinoma was identified as a negative independent predictive factor for central LNM [20]. However, more often, lateral LNM with Hashimoto's thyroiditis is found in patients with PTMC [21]. Univariate and multivariate analyses revealed that underlying Hashimoto's thyroiditis was statistically significant with lateral LNM in our study. Central LNM was proved to be an important independent factor for lateral LNM in several studies [17, 18, 22]. In our study, central LNM was proven to be intraoperative important information in predicting for lateral LNM confirmed by frozen biopsy ($P < 0.001$). A recent report has shown that quantitative evaluation of the central compartment, identified by frozen biopsy, can be performed in less than 30 min [18]. The mean number of positive central lymph nodes is greater in patients with lateral LNM than in those without (5.3 vs. 3.2; $P = 0.004$); patients with lateral LNM have a higher central lymph node metastatic ratio (the ratio of the number of positive central lymph nodes to the number of total acquired lymph nodes dissected from the central compartment) than patients without (mean 49 vs. 37 %), but the difference is not statistically significant [18]. Unfortunately, we could not analyze the number of positive central lymph nodes or the central lymph node metastatic ratio identified by frozen biopsy because of the limitations of frozen data collection. In our study, we only evaluated the status, having metastasis or not, of the central neck. Further study will be needed to evaluate the association of central lymph nodes in the prediction of lateral LNM.

In our study, multivariate analysis of US features showed that upper pole location was an independent predictive factor for lateral LNM, which was similar to two other reports [17, 22]. The result may be explained by the hypothesis that carcinoma cells from the upper region are more likely to be transported to the lateral lymph nodes by lymphatic flow along the superior thyroid artery [23]. In this study, contact of >25 % with the adjacent capsule was not an independent factor for lateral LNM, although it was statistically significant on univariate analysis. The number of ill-defined margins in patients with lateral LNM was significantly greater than that in patients without it, which was supported by those reports [24, 25]. Microcalcifications are the most important predicting factor for PTMC [26]. Previous studies have found that the presence of calcifications was an independent factor for lateral LNM [17, 22]. Microcalcifications are associated US features on US-diagnosed lateral LNM, while coarse or no calcifications in PTMC have no association with lateral LNM [25]. In our study, the presence of calcifications was an independent predictive factor of lateral LNM, and microcalcifications occurred more frequently than other calcifications in patients with lateral LNM, similar to that in a previous article [18].

The risk of neck recurrence increases 6.5-fold in the presence of LNM, and 80 % of patients with neck LNM have distant metastasis [30]. Takamura Y et al. [27] have shown that patients with lateral LNM are more likely to develop recurrence. Recurrence may not be associated with increased mortality, but repeated operation increases the incidence of operative complications (damage of laryngeal nerve, hypoparathyroidism, and so on) and medical costs. When lateral LNM is obvious or preoperatively diagnosed definitively, the surgical extent of lymph node can be easily established. However, when the status of lateral lymph nodes is not adequate or obvious, we need more information to differentiate between patients with and without lateral LNM. Previous studies have shown that US is an important tool in the detection of metastatic nodes with high specificity and positive predictive value [28]. However, US has limitations including that the results show variable sensitivities (37–84 %) and the difficulty in evaluating deep lymph nodes, such as retropharyngeal and mediastinal nodes [29, 30]. To improve the diagnostic accuracy, we used a combination of clinicopathologic features and US findings. Enlightened by a US scoring system in predicting malignancy of thyroid nodules [31], we developed a scoring system of clinicopathological and US features on the basis of multiple logistic regression analysis. Using ROC curves, we identified the clinicopathological and US index points ≤ 2 as the best for detection of lateral LNM negativity with a sensitivity of 83.3 %, positive predictive value of 89.6 % and negative predictive value of 72.9 %.

This study was designed to evaluate the value of a scoring system according to the preoperative and intraoperative clinicopathological and US features in predicting the status of the lateral compartment. The scoring system of clinicopathological and US features can be helpful for surgeon to decide the essential surgical strategy for each patient. However, there are several potential limitations in this study. First, we had not collected all the pathologic data such as the number of positive central lymph nodes because of the low sensitivity and specificity by frozen biopsy. Second, there were no long-term follow-up results, including disease recurrence, disease-free survival, and so on for confirming whether the scoring system is useful for treatment outcome.

Conclusions

The scoring system of clinicopathological and US features for the prediction of lateral LNM can be another diagnostic approach when the results of preoperative diagnostic evaluation for lateral LNM are not adequate or obvious. Patients with clinicopathological and US index points ≤ 2 could be considered as lateral LNM negative. More aggressive diagnostic approaches are needed for clinicopathological and US index points >2.

Conflict of interest There is no financial relationship that might lead to a conflict of interest in relation to the manuscript.

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