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ORIGINAL RESEARCH

Preoperative Sonographic and Clinicopathological Predictors for Solitary Lateral Neck Node Metastasis in Papillary Thyroid Carcinoma: A Retrospective Study

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Background: Cervical lymph node metastasis (LNM) is an independent risk factor for poor prognosis of papillary thyroid carcinoma (PTC), but the scope of PTC lateral neck dissection (LND) is controversial. Solitary lateral lymph node metastasis (SLNM) is a special type of PTC with lateral LNM. Currently, study on the preoperative clinical characteristics of SLNM has been seldomly reported. This study evaluated the preoperative characteristics for predicting the SLNM of PTC.

Methods: We included 391 patients diagnosed with PTC between May 2011 and July 2017. Among those patients, 44 had SLNM and 347 had multiple lateral neck node metastasis (MLNM). The clinicopathologic characteristics and other central lymph node metastasis risk factors were retrospectively analyzed.

Results: Univariate analysis revealed that age and tumor size (≤1 cm) were significantly correlated with SLNM. In ROC curve analysis, the optimal cutoff age of preoperative predictors for the prediction of SLNM was 46.5 years (AUC=0.623, 0.536–0.710). Besides, the frequency and mean number of CLNM was significantly less in the SLNM than MLNM group. The oval and round tumor shape and well-defined margin of the tumor were more common in the SLNM group (p =0.001; p=0.024, respectively). In addition, multivariate analysis revealed that age ≥47, capsular invasion, no extrathyroidal extension, with central lymph node metastases and irregular shape were independent SLNM predictors of PTCs (odds ratio 2.386, 0.173, 0.284, 0.239, 0.188; 95% CI 1.07–5.140, 0.058–0.840, 0.066–0.926, 0.091–0.437, 0.167–0.864, respectively).

Conclusion: This study supported that SLNM is more likely to happen in PTC patients with age ≥47 years, capsular invasion, no extrathyroidal extension, with central lymph node metastases and irregular shape. That denotes, selective single level neck dissection can be considered as an alternative to systemic lateral neck dissection in those patients.

Keywords: solitary lateral lymph node metastasis, papillary thyroid carcinoma, central lymph node dissection

Introduction

Thyroid cancer is one of the most common endocrine tumors, and its incidence is increasing gradually.[1–4] Papillary thyroid carcinoma (PTC) is the most common pathological type of thyroid cancer, though with a low degree of malignancy, prone to cervical lymph node metastasis (LNM).[5] Cervical LNM rate is approximately 30~80%, while, lateral LNM rate is up to 64.2%.[6,7] Central lymph node metastasis

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(CLNM) has been proved to be an independent risk factor for local recurrence[8–10] and decreased survival rate.[11–13] At present, surgery is the main treatment for cervical LNM. As the pattern of clinical LNM varies,[6,14,15] the scope of dissection is still controversial. A wide range of surgical dissection can lead to the risk of postoperative complications and reduce the quality of life after surgery, on the contrary, if the scope of lateral neck dissection (LND) is too small, postoperative recurrence will lead to the second operation. Therefore, it is necessary to analyze the characteristics of cervical lymph node metastasis for guiding surgery and preventing surgical complications.

Decisions about the scope of surgery are usually based on predictable patterns of LNM. Multiple lateral neck node (MLN) metastasis refer to the number of positive lymph nodes in the lateral regions more than two. LND including levels II to V is generally recommended for complete clearance of MLNM. However, there are different opinions on the dissection scope of solitary lateral neck node (SLN) metastasis. SLN metastasis is a special phenomenon in PTCs, in which patients have only one lateral lymph node metastasis regardless of central LNM or not. Therefore, various types of LND were proposed.[16–18] If a large-scale LND is performed on a PTC patient with SLNM, it may result in increased postoperative complications, including secondary nerve injury, hypoparathyroidism, chylous leakage, skin numbness around the ear, neck and shoulder, and a decline in quality of life.[19–21] It was expected that clinical features would be related to the SLN metastasis, and an attempt was made to find a relationship between clinical features and SLN metastasis.

For better distinction of SLNM and choices of surgical method in PTC patients, in our current analyses, 391 PTC patients were divided into SLNM and MLNM groups according to the number of LNM from postoperative histopathologic records, and identify the risk factors associated with SLNM in PTC by investigating preoperative clinicopathological and ultrasound clinical features retrospectively.

Methods

Ethics Statement

Approval to retrospectively review the medical records of patients was obtained from the Ethics Committee of Xiangya Hospital, Central South University and conducted according to the principles expressed in the Declaration of Helsinki. In addition to approving the study protocol, the Ethics Committee required neither patient approval nor informed consent for the review of records. Furthermore, we confirmed that the data related to this manuscript was anonymized.

Patients

Initially, 493 patients with pathologically confirmed LNM who underwent curative initial surgery with neck dissection for PTC between May 2011 and July 2017, were retrospectively screened. Patients with the following conditions were excluded: (1) other types of thyroid cancer; (2) a history of previous thyroidectomy; (3) previous neck radiotherapy history, patients without sufficient clinical and ultrasound data. SLNM of PTC was defined as patients who were confirmed having only one lateral lymph node metastasis. Only the data for which both preoperative ultrasound findings and postoperative pathologic reports were available were included. Finally, a cohort of 391 patients was analyzed. All patients underwent simultaneous total thyroidectomy (TT), bilateral central neck dissection (CND), and LND (at least from levels II to V). Among the study subjects, 44 (11.3%) patients were in the SLNM group, and 347 (88.8%) patients were in the MLNM group. All the participants in this study signed the written consent before surgery.

Clinicopathological Parameters

The preoperative sonographic and clinicopathological characteristics between two groups were analyzed. Preoperative clinical parameters included age, sex, number of tumors, capsular invasion, extrathyroidal extension, lymphocytic thyroiditis, TSH level, CLNM, number of CLNM. Chemiluminescence immunoassay was used to determine serum TSH, and the reference range was 0.27~4.2mIU/L. Ultrasound findings, including tumor size, lymphadenopathy, location, shape, margin, echogenicity, and calcification were evaluated. We defined the maximum diameter as tumor size, when patient was found with multiple foci, the dimension of the largest PTC lesion was recorded. Tumor location was classified as the superior, middle, or inferior third of the thyroid gland. Shape of the nodule was defined as having an irregular shape or oval and round. Margin was defined as poorly or well defined. Echogenicity was defined as hypoechogenic or other echogenic. In our study, other types of echogenicity included isoechoic, mixechoic and hyperechoic.

Statistical Analysis

Statistical software SPSS 22.0 was used to analyze the data. Continuous variables are presented as mean ± standard deviation. Pearson's chi-squared test and the Student's *t*-test were used to compare the correlation between preoperative clinicopathological and ultrasound features of PTCs with lateral LNM. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff points for patient age, tumor sizes and number of CLNM in the prediction of solitary and multiple lateral neck metastasis. Univariate analysis and multivariate analysis were performed by binary logistic regression to evaluate the predictors for SLNM in PTCs. All p-values were two-sided, and p-values of <0.05 were considered statistically significant.

Results

Clinicopathological and Sonographic Characteristics of Study Subjects

A total of 391 patients was analyzed, of which there were 124 (31.7%) male and 267 (68.3%) female, and their mean age was 36.92±12.88 years (range 9 to 77 years). The clinicopathological characteristics of the patients in two groups are presented in Table 1. The median age of SLNM group and MLNM group were 41.56±12.39 years and 36.22±12.56 years, with significant difference between the groups ($p < 0.05$). In this study, 64 (16.4%) patients with PTC had skipped metastasis, and skipped LNMs were significantly more frequent in SLNM group than in MLNM group (43.2% versus 13.0%, $p < 0.001$). Besides,

Table 1 Clinicopathological Characteristics of Study Subjects

Clinical Characteristics	Total (n=391)	SLNM Group (n=44)	MLNM Group (n=347)	*p* value[a]
Age (9~77 years)	36.92±12.88	41.56±12.39	36.22±12.56	0.008[b]
Sex				
Male	124(31.7%)	17(38.6%)	107(30.8%)	0.295
Female	267(68.3%)	27(61.4%)	240(69.2%)	
Number of tumors				
Solitary	246(62.9%)	33(75%)	213(61.4%)	0.078
Multifocality	145(37.1%)	11(25%)	134(38.6%)	
Tumor size (0.1~9.7 cm)	2.14±1.31	2.08±1.48	2.23±1.29	0.461[b]
>1cm	326(83.4%)	32(72.3%)	294(84.7%)	0.044
≤1cm	65(16.6%)	12(27.3%)	53(15.3%)	
Capsular invasion				
Present	129(33%)	12(27.3%)	117(33.7%)	0.392
Absent	262(67%)	32(72.3%)	230(66.3%)	
Extrathyroidal extension				
Present	115(29.4%)	15(34.1%)	100(28.8%)	0.470
Absent	276(70.6%)	29(65.9%)	247(71.2%)	
Lymphocytic thyroiditis				
Present	146(37.3%)	15(34.1%)	131(37.8%)	0.636
Absent	245(62.7%)	29(65.9%)	216(62.2%)	
TSH level				
High	59(15.1%)	6(13.6%)	53(15.3%)	0.658
Normal	322(82.4%)	36(81.8%)	286(82.4%)	
Low	10(2.5%)	2(4.6%)	8(2.3%)	
Number of CLNM	2.37±2.27	1.64±2.27	3.84±4.64	0.000[b]
CLNM				
Present	327(83.6%)	25(56.8%)	302(87.0%)	0.000
Absent	64(16.4%)	19(43.2%)	45(13.0%)	

Notes: [a]Pearson's chi-squared test was adopted; [b]The Student's *t*-test was adopted.

Abbreviations: SLNM, solitary lateral neck node metastasis; MLNM, multiple lateral neck node metastasis; TSH, thyroid stimulating hormone; CLNM, central lymph node metastasis.

the mean number of central lymph node metastasis (CLNM) was lower in the SLNM than in the MLNM group (1.64±2.27 versus 3.84±4.64; $p < 0.001$).

The analysis of preoperative sonographic features is listed in Table 2. In this study, ultrasonography (US) did not find a single lymph node enlargement in the lateral cervical region. And the difference in lymphadenopathy on neck US between the two groups was not statistically significant ($p>0.05$). In receiver operating characteristic (ROC) curve analysis, we found tumor size would be a well predictor for MLNM. The optimal cutoff tumor sizes in MLNM group were 1.15 cm (area under curve (AUC) =0.554, 0.459–0.648) (Figure 1). While, we found that papillary thyroid microcarcinoma (PTMC) (tumor sizes≤1 cm) was more common in the SLNM group than in the MLNM group ($p = 0.044$). An oval and round tumor shape was more common in the SLNM group (63.6%) than in the MLNM group (37.5%, $p =0.001$). The well-defined margin of the tumor was also significantly more frequent in the SLNM group (63.6% versus 45.5%, $p=0.024$). No significant differences in location and calcification of the tumor were found between two groups.

Optimal Cutoff of Preoperative Predictors for the Prediction of SLNM and MLNM

In order to evaluate the value of age, numbers of CLNM and tumor size in predicting SLNM or MLNM, ROC curve analysis was calculated. In our results, the area under the curve of age in SLNM group was 0.623 (the optimal cutoff age was 46.5 years), indicating that the accuracy of the test was good, which means the age≥47 was a well predictor of SLNM (Figure 2). The cutoff value of the numbers of CLNM predictors for MLNM was defined as 1.5 (AUC=0.753, 0.681–0.826), and the optimal cutoff tumor size in MLNM was 1.15 cm (AUC=0.554, 0.459–0.648) (Figure 1). PTC patients with two or more central lymph node metastasis and tumor size ≥1.15 cm was at high risk for MLNM.

Multivariate Analysis of Risk Factors Related to Solitary Lateral Neck Metastasis

To define the predictors of SLNM of PTCs, we performed binary logistic regression analyses with clinicopathological

Table 2 Sonographic Characteristics of Study Subjects

Clinical Characteristics	Total (n=391)	SLNM Group (n=44)	MLNM Group (n=347)	*p* value[a]
Lymphadenopathy on neck US				
Present	353(90.3%)	41(93.2%)	312(91.0%)	0.491
Absent	38(9.7%)	3(6.8%)	35(9.0%)	
Location of the tumor on neck US				
Superior lobe	125(32%)	15(34.1%)	110(31.7%)	0.869
Middle lobe	146(37.3%)	17(38.6%)	129(37.2%)	
Inferior lobe	120(30.7%)	12(27.3%)	108(31.1%)	
Shape of the tumor on neck US				
Irregular shape	233(59.6%)	16(36.4%)	217(62.5%)	0.001
Oval and round	158(40.4%)	28(63.6%)	130(37.5%)	
Margin of the tumor on neck US				
Poorly defined	205(52.4%)	16(36.4%)	189(54.5%)	0.024
Well defined	186(47.6%)	28(63.6%)	158(45.5%)	
Echogenicity of the tumor on neck US				
Hypoechogenic	260(66.5%)	29(65.9%)	231(66.6%)	0.930
Other echogenic	131(33.5%)	15(34.1%)	116(33.4%)	
Calcification of the tumor on neck US				
Present	376(96.2%)	43(97.7%)	333(96.0%)	0.567
Absent	15(3.8%)	1(2.3%)	14(4.0%)	

Note: [a]Pearson's chi-squared test was adopted.
Abbreviations: SLNM, solitary lateral neck node metastasis; MLNM, multiple lateral neck node metastasis; US, ultrasonography.

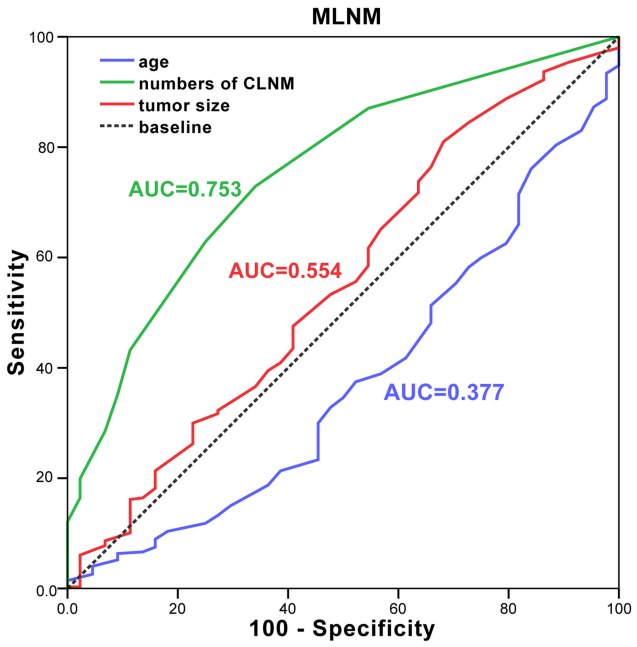

Figure 1 ROC curve for age (blue line), tumor sizes (red line) and number of CLNM (green line) in the prediction of MLNM.
Abbreviations: ROC, receiver operating characteristic; MLNM, multiple lateral neck node metastasis; CLNM, central lymph node metastasis; AUC, area under curve.

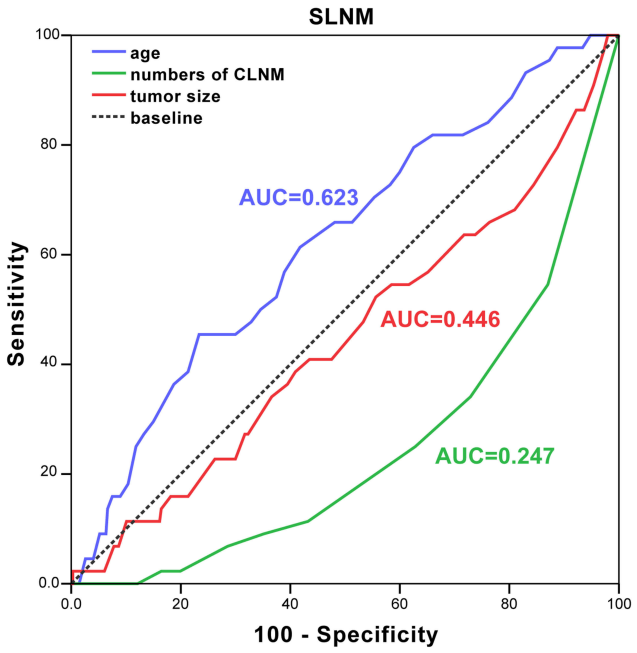

Figure 2 ROC curve for age (blue line), tumor sizes (red line) and number of CLNM (green line) in the prediction of SLNM.
Abbreviations: ROC, receiver operating characteristic; CLNM, central lymph node metastasis; AUC, area under curve; SLNM, solitary lateral neck metastasis.

and US features (Table 3). We found that age ≥47 years was significant predictors of SLNM (OR=2.386, p=0.026). However, capsular invasion, no extrathyroidal extension, with central lymph node metastases and irregular shape

Table 3 Multivariate Analysis of Risk Factors Related to Solitary Lateral Neck Metastasis

Variables	OR	95% CI	*p* value
Patients' age ≥47 years	**2.386**	**1.07–5.140**	**0.026**
Male gender	1.828	0.858–3.896	0.118
Tumor size < 1cm	0.463	0.168–1.272	0.135
Capsular invasion	**0.220**	**0.058–0.840**	**0.027**
No extrathyroidal extension	**0.247**	**0.066–0.926**	**0.038**
Lymphocytic thyroiditis	1.240	0.569–2.702	0.588
With central lymph node metastases	**0.200**	**0.091–0.437**	**0.000**
Lymphadenopathy of the tumor on neck US	1.966	0.485–7.969	0.344
Irregular shape	**0.380**	**0.167–0.864**	**0.021**
Poorly defined margin of the tumor	0.653	0.283–1.507	0.318

Note: Variables with statistical significance were shown in bold.
Abbreviations: US, ultrasonography; OR, odds ratio; CI, confidence interval.

were statistically significant differences (OR=0.220, p=0.027; OR=0.247, p=0.038; OR=0.200, p=0.000 and OR=0.380, p=0.021, respectively). As can be seen from the results, these factors were all protective factors for SLN metastasis in PTC patients. In other words, they were risk factors of PTC patients with MLNM and in the presence of these factors, lateral regional lymph node dissection should be performed.

Discussion

Our study is the first time to evaluate preoperative sonographic and clinicopathological characteristics for predicting SLNM in PTC patients. We found that age ≥47 years, capsular invasion, no extrathyroidal extension, with central lymph node metastasis and irregular shape were significantly associated with SLNM. Multivariate analysis showed that patients' age ≥47 years was the risk of SLNM. Nevertheless, capsular invasion, no extrathyroidal extension, with central lymph node metastasis and irregular shape were identified as protective factors for SLNM in PTC patients. In the absence of the above characteristics, there was a high possibility of SLNM.

The effect of age on lateral LNM remained contradictory. Age under 45 years has been reported to be associated with lateral LNM,[22] while, age ≥45 years was considered to be an independent risk factor for LNM in the PTC with lateral lymph node metastasis.[23,24] In this study, age ≥47 years was considered as a strong marker for predicting SLNM.

Studies have shown that extrathyroidal extension is a risk factor for lateral LNM.[5,25] However, the absence of capsular invasion could also be a predictor of SLNM.[26]

Similarly, we found in this study that when the tumor invaded the capsule but no extrathyroidal extension was present, the risk of SLM metastasis was reduced. Hence, PTC with SLN metastasis may be in a special biological state. Therefore, preoperative evaluation of the lateral cervical lymph nodes should be conducted carefully, and selective single regional lymph node dissection should be considered.

LNM is a risk factor for recurrence in PTC.[27,28] Lymph node dissection can significantly improve prognosis, so lymph nodes should be carefully evaluated before surgery. At present, there is still no clear suggestion on the scope of lateral neck dissection. Emerging study has attempted to evaluate preoperative sonographic and clinicopathological characteristics predicting SLNM of PTC. Some studies reported that tumor size, location and the number of central LNM were risk factors for lateral LNM.[5,29] When the positive number of central lymph node metastasis were two or more, the metastatic rate of lateral LNM was 70.0 ~ 93.3%.[30] In this analysis, the ROC curve showed that the optimal cutoff value of central LNM was 1.5. This result is consistent with many previous studies. However, in the current series, location was not found to be associated with the number of lateral LNM. Whereas, without central metastases, the lateral LNM can also occur in PTC patients, known as skip metastasis.[27] This study found that skip metastasis was more common in patients with SLNM than in patients with MLNM, supported by previous reports.[26,31] ROC curve analysis determined that 1.15 cm was an optimal tumor size cutoff for predicting MLNM.

The preoperative US features of PTC patients were also evaluated, and their clinical significance for predicting SLNM was analyzed. Oval and round shape and well-defined tumor were associated with SLN metastasis. These findings suggest that differences in the US findings may reflect different pathological properties in PTC patients with MLNM. The multivariate analysis showed that irregular shape was a protective factor for SLNM. On the contrary, its presence suggested a high risk of MLNM.

According to our results, low-risk PTC characteristics in terms of small primary tumor size and no extrathyroidal extension were shown in patients with SLNM. Low-risk patients carry a lower risk of cancer mortality and recurrence.[28,32] Extensive dissection in these patients will increase the risk of complications, for instance, accessory nerve injury, chyle leakage, skin numbness around the ear, neck and shoulder.[33–36] When performing lymph node dissection, it is necessary to make clear the scope of dissection, grasp the clear anatomical hierarchy, and protect the vascular branches and nerves. Therefore, in order to ensure the surgical benefit of patients, single regional or several sub-regional lymph node dissections is feasible for PTC patients with SLNM.

This study has some notable limitations, including those inherent to its retrospective design. For patients with occult metastases, we did not perform preventive LND, so we could not determine the true incidence of SLNM. Although preoperative lymph node status was evaluated, we were unable to determine whether prophylactic lateral neck dissection improved patient outcome.[26] In this study, there was no comparison of ultrasonic characteristics of lymph node, which could be further studied in the future. Despite these limitations, the main advantage of this study is that we evaluated the preoperative characteristics of SLNM in order to decide on whom to perform selective single regional LND, which could provide the basis for the future prediction model.

Conclusion

The results of our study indicate that age≥47 years, capsular invasion, no extrathyroidal extension, with central lymph node metastases and irregular shape were protective factors for SLNM in PTC patients. Selective single regional or several sub-regional LND can be considered in PTC patients with SLNM, whom with small primary tumor size (≤1 cm) and no extrathyroidal extension were in low risk.

Abbreviations

LNM, lymph node metastasis; PTC, papillary thyroid carcinoma; SLNM, solitary lateral lymph node metastasis; MLNM, multiple lateral neck node metastasis; CLNM, central lymph node metastasis; SLN, solitary lateral lymph node; MLN, multiple lateral neck node; LND, lateral neck dissection; TT, total thyroidectomy; CND, central neck dissection; CI, confidence interval; US, ultrasonography; OR, odds ratio; ROC, receiver operating characteristic; AUC, area under curve; PTMC, papillary thyroid microcarcinoma; TSH, thyroid stimulating hormone.

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Disclosure

The authors declare no conflicts of interest in this work.

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