

Combining Clinicopathologic and Ultrasonic Features for Predicting Skip Metastasis of Lateral Lymph Nodes in Papillary Thyroid Carcinoma

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Background: Skip metastasis, regarded as lateral lymph node metastasis (LLNM) without involving the central lymph node metastasis (CLNM), in papillary thyroid carcinoma (PTC) patients is commonly unpredictable. The purpose of the present research was to investigate the independent risk factors of skip metastasis in patients with PTC.

Methods and Materials: In the present research, 228 consecutive PTC patients who experienced total thyroidectomy coupled with central and lateral lymph node dissection from May 2020 to September 2022 at the Affiliated hospital of Jiangsu University were included in our research. Univariate and multivariate analysis were then applied to investigate the risk factors of skip metastasis in patients with PTC. Furthermore, a predictive model of skip metastasis was then constructed based on risk factors.

Results: The skip metastasis rate was 11.8% (27/228) in the current research. After the univariate and multivariate analysis, tumor size ≤ 10 mm, unilaterality, microcalcification, and upper tumor location were determined to be predictive factors of skip metastasis. The risk score of skip metastasis was calculated: risk score = $1.229 \times (\text{if tumor nodule} \leq 10\text{mm}) + 1.518 \times (\text{if unilaterality nodule}) + 1.074 \times (\text{if microcalcification in nodule}) + 2.332 \times (\text{if nodule in upper location})$.

Conclusion: Tumor size ≤ 10 mm, unilaterality, microcalcification, and upper tumor location can increase the occurrence of skip metastasis in patients with PTC, which is expected to provide useful information to guide the suitable intraoperative window.

Keywords: skip metastasis, papillary thyroid carcinoma, ultrasonic features, clinicopathologic factors, lateral lymph node metastasis

Introduction

The thyroid gland, made up of two joint lobes, weighs 20 to 30 grams in human, which is one of the largest endocrine glands in the human body. Thyroid nodules are common in the thyroid gland and the prevalence ranges from 4% to 7%. Most of these patients are asymptomatic and have normal thyroid hormone secretion.¹ Papillary thyroid carcinoma (PTC) is frequent endocrine disease with the increasing incidence worldwide, which is mainly attributed to the widespread utilization of high-resolution ultrasound (US) and US-guided fine-needle aspiration (FNA) biopsy.²⁻⁵ The number of newly diagnosed PTC cases in 2020 was as high as 586,000, accounting for 11/36 newly diagnosed malignant cancers with the increased 3% incidence annually.^{6,7} An abundance of evidence has shown that most cervical lymph nodes metastasis in PTC patients happens in a stepwise fashion.⁸ Metastatic cervical lymph nodes initially involve the central compartment, subsequently progress to the ipsilateral lateral compartment, and ultimately extend to the contralateral lateral and mediastinal compartment.^{9,10} The metastatic progression is helpful to provide the useful information to select the suitable surgery scope. However, the skip metastasis, regarded as lateral lymph node metastasis (LLNM) without involving the central lymph node metastasis (CLNM), can be developed in some PTC patients.^{11,12} The benefits of preventive lateral lymph node dissection (LLND) for PTC patients without the clinical evidence of LLNM persist a great

deal of controversies. Some claims that preventive LLND may escalate the risks of surgical complications and medical cost burden, while the other argues preventive LLND can effectively reduce the recurrence and metastasis of PTC, thereby avoiding the secondary operation.^{13,14} Hence, it is urgent demand to precisely assess the status of skip metastasis, which is helpful to guide the optimal surgical window.

Ultrasound (US) is usually performed for the imaging examination of metastatic cervical lymph nodes in PTC patients in the clinical work.¹⁵ However, the capability of US to recognize the interventricular lymph nodes is often restricted attributed to the overlying thyroid gland, with a sensitivity of only 20% to 40% for US detecting.^{16,17} It is difficult for visualize LLNM in the condition of without CLNM.^{18,19} US-guided fine-needle aspiration (FNA) is commonly performed to enhance the diagnostic accuracy through the cytologic specimen. As we all know, B-type Raf (BRAF) mutation is a somatic alteration that results in oncogenic activation of the MAPK signaling pathway and usually associates with the development, proliferation and metastasis of PTC.^{20,21} Preoperative detection of BRAF^{V600E} mutation from the US-FNA specimen can potentially guide the initial operative scope.²²

In the current research, 228 PTC consecutive patients, including 61 male and 167 female participants, with the average age of 44.46 years old, who accepted the thyroidectomy coupled with CLND and LLND were retrospectively reviewed in our study. Univariate and multivariate logistic regression were applied to identify the independent predictors of skip metastasis in PTC patients. The prediv model was constructed from these independent predictors, which is expected to propose individualized treatment strategies to help clinicians to make appropriate clinical decisions.

Methods and Materials

Our study design followed the international regulations based on the Declaration of Helsinki. Our research was approved by the Ethical Committee of the Affiliated Hospital of Jiangsu University (SWYXLL20190225-2) and written informed consent was required from participants.

Enrolled Patients

Our retrospective research originally enrolled PTC participants who accepted the total thyroidectomy coupled with LLND and CLND from May 2020 to September 2022 at the Affiliated Hospital of Jiangsu University. All participants were confirmed to be PTC with LLNM through postoperative pathology. Of note, the exclusion criteria included: (a) the history of neck surgery or radiation; (b) incomplete information of PTC; (c) nodules diagnosed as other types of thyroid carcinomas in pathology; (d) refusal to BRAF^{V600E} analysis. The most suspicious or the largest nodule was selected into the following study when PTC participants have multifocal tumors.

US Evaluation

The My Lab Twice Color Doppler ultrasound systems with a probe frequency of 7 to 13 MH was utilized for PTC examination in the current research. The US images of the targeted PTC were observed longitudinally and transversely on the gray-scale modality. These collected US graphs were independently evaluated by two radiologists with more than 5-year working experience who did not know any information about the PTC participants. Another senior radiologist with more than 15-year working experience, who was blinded to information including patient identity, pathologic and molecular marker results, re-evaluated the US characteristics and made the final decision when the disagreements appeared. These US features of targeted PTC were interpreted: tumor size (>10 mm/ ≤10 mm in diameter), tumor location (upper, middle, and lower), multifocality (absent/present), bilaterality (absent/present), solid component (absent/present), hypo-echogenicity (absent/present), microcalcification (absent/present), margin (ill-defined/defined), shape (irregular/regular), and taller-than-wide shape (absent/present).

Thyroidectomy with Neck Dissection

All PTC participants have experienced the total thyroidectomy with preventive CLND and LLND. Lateral compartment comprises levels II to V. According to the American Thyroid Association (ATA) guidelines, the modified LLND was performed including the level II–V. The level I dissection was conducted only when imaging, cytopathology, or

intraoperative findings indicated suspicious node metastasis. Harmonic scalpel (HS) was performed in the thyroidectomy, which is more effective at achieving haemostasis.²³

BRAF Mutation Analysis

BRAF mutation was reported to be closely associated with the aggressive histopathologic features such as ETT and cervical LNM. The samples required from preoperative fine-needle aspiration of targeted PTC were stored in preservation solution, which was then submitted to a genetic detection company for BRAF mutation analysis. The polymerase chain reaction (PCR) conditions and primers for amplifying exon 15 in BRAF containing V600E mutation were established previously. Genomic DNA was extracted from cytologic specimens through the QIAamp DNA FFPE Tissue Kit (QIAGEN) following the manufacturer's instruction.

Histopathologic Analysis

Histopathologic variables were analyzed based on postoperative pathological examination including tumor staging, histological subtypes, extrathyroidal extension (ETE), coexistence of nodular goitre, and coexistence of Hashimoto's thyroiditis. Histopathologic data was analyzed by an experienced pathologist with more than 5-year working experience. With the use of frozen sections from the surgery, histopathologic findings were ultimately analyzed. Haematoxylin-eosin staining and immunohistochemistry were used to confirm the result.

Statistical Analysis

All statistical analysis was implemented by the SPSS software (ver. 23.0; SPSS Inc., Chicago, IL, USA). The comparisons of categorical were analyzed by Pearson χ^2 or Fisher's exact test, and the comparisons of continuous variables were analyzed by the independent *T*-test. Furthermore, multivariate logical analysis was performed to determine the risk factors of skip metastasis. Receiver operating characteristic (ROC) curve was constructed to determine the optimal cut-off value. The area under curve (AUC) value of ROC was used to examine the discriminatory power of our prediction model. The 2-tailed *P* value of less than 0.05 was considered statistically significant.

Results

Enrolled Participants Characteristics

After the strict screening, 228 PTC participants were ultimately included into our research. Skip metastasis of lateral lymph nodes occurred in 27 (11.8%) cases in these PTC participants, and no skip metastasis was detected in other participants. Of the participants, 61 (26.8%) participants were male, and 167 (73.2%) participants were female. The average age was 44.46 years old, and the range of age was between 18 and 76 years old. There are 141 (61.8%) participants were <55 years old, and 87 (38.2%) were 55 years and older. Briefly, 117 (51.3%) PTC patients harbored bilaterality PTC, whereas 111 (48.7%) participants did not. In 89 (39.0%) PTC participants, the diameter of PTC ≤ 10 mm was in 89 (39.0%) patients, and the diameter > 10 mm was in 139 (61.0%) PTC patients. Multifocality was detected in 100 (43.9%) participants and 90 (39.5%) were in the location of upper lobe. Suspicious US characteristics, including solid component, hypo-echogenicity, microcalcification, irregular shape, ill-defined margin and taller than wide shape were exhibited in 224 (98.2%), 196 (86.0%), 88 (38.7%), 122 (53.5%), 121 (53.1%) and 67 (29.4%) of PTC cases, respectively. 54 (23.7%) and 51 (22.4%) participants were concomitant Hashimoto's thyroiditis and extrathyroidal extension (ETE), respectively. Typically, BRAF^{V600E} mutation from FNA cytologic specimen was found in 137 (60.1%) PTC participants. The demographic, ultrasonic and clinicopathological characteristics of included participants were summarized in Table 1. In addition, according to the eighth edition AJCC staging system, the age of 55 years was considered as a cutoff point for demarcating age-related survival in most thyroid cancer staging systems.^{24,25} The incidence of skip metastasis in PTC was 14.2% (20/141) and 9.8% (6/61) in the age <55 years group and male sex group, respectively.

Table 1 Comparison of the Clinicopathologic and US Features Between the Absence and Presence of Skip Metastases in PTC Patients. P value < 0.05 was Highlighted in Bold Font.

Characteristics	Skip Metastasis (N=228)		P value
	Positive (N=27)	Negative (N=201)	
Age			P=0.163
<55 years	20 (74.1%)	121 (60.2%)	
≥55 years	7 (25.9%)	80 (39.8%)	
Gender			P=0.571
Male	6 (22.2%)	55 (27.4%)	
Female	21 (77.8%)	146 (72.6%)	
Tumor size			P<0.001
≤10 mm	19 (70.4%)	70 (34.8%)	
>10 mm	8 (29.6%)	131 (65.2%)	
Multifocality			P=0.373
Multifocal	14 (51.9%)	86 (42.8%)	
Unifocal	13 (48.1%)	115 (57.2%)	
Bilaterality			P=0.046
Absent	18 (66.7%)	93 (46.3%)	
Present	9 (33.3%)	108 (53.7%)	
Internal component			P=0.398
Solid	26 (96.3%)	198 (98.5%)	
Cystic	1 (3.7%)	3 (1.5%)	
Hypo-echogenicity			P=1.000
Present	23 (85.2%)	173 (86.1%)	
Absent	4 (14.8%)	28 (13.9%)	
Microcalcification			P=0.006
Present	17 (63.0%)	71 (35.3%)	
Absent	10 (37.0%)	130 (64.7%)	
Shape			P=0.523
Irregular	16 (59.3%)	106 (52.7%)	
Regular	11 (40.7%)	95 (47.3%)	
Margin			P=0.893
Ill-defined	14 (51.9%)	107 (53.2%)	
Defined	13 (48.1%)	94 (46.8%)	
Taller than wide			P=0.632
Present	9 (33.3%)	58 (28.9%)	
Absent	18 (66.7%)	143 (71.1%)	
Location			P<0.001
Upper	20 (74.1%)	70 (34.8%)	
Non-upper	7 (25.9%)	131 (65.2%)	
Hashimoto's thyroiditis			P=0.501
Concomitant	5 (18.5%)	49 (24.4%)	
Non-concomitant	22 (81.5%)	152 (75.6%)	
Extrathyroidal extension			P=0.985
Present	6 (22.2%)	45 (22.4%)	
Absent	21 (77.8%)	156 (77.6%)	
BRAF mutation			P=0.046
Positive	21 (77.8%)	116 (57.7%)	
Negative	6 (22.2%)	85 (42.3%)	

Univariate Analysis

It is well known that solid composition, hypo-echogenicity, microcalcification, irregular shape, ill-defined margin, and taller-than-wide shape were considered as malignant US features in PTC.²⁶ Moreover, BRAF mutation is usually

Table 2 Multivariate Logistic Regression Analysis in Predicting Skip Metastasis of LLNM in PTC Patients. P value < 0.05 was Highlighted in Bold Font.

PTC Characteristics	β Coefficient	Odds ratio	95% Confidence Interval	P value
Tumor size ≤ 10 mm	1.229	3.417	1.250–9.343	0.017
Unilaterality	1.518	4.562	1.017–20.468	0.048
Microcalcification	1.074	2.927	1.087–7.879	0.034
Upper location	2.332	10.303	2.290–46.353	0.002
BRAF mutation	0.193	1.213	0.341–4.321	0.766

associated with the aggressiveness of PTC.²² As the vividly exhibited in Table 1, the diameter of PTC ≤ 10 mm have a higher frequency of skip metastasis than those larger than 10 mm (70.4% vs 34.8%, CI 1.852–10.688, $P < 0.001$). In addition, microcalcification (CI 1.353–7.159, $P = 0.006$) was obviously associated with the presence of skip metastasis in PTC participants. Other malignant US features, including solid component, hypo-echogenicity, irregular shape, ill-defined margin, and taller than wide shape were not remarkably correlated with the skip metastasis in patients with PTC (P value > 0.05). Skip metastasis was significantly associated with unilaterality PTC (CI 0.996–5.417, $P = 0.046$) and upper location (CI 2.156–13.261, $P < 0.001$). BRAF^{V600E} mutation was also inclined to appear the skip metastasis (CI 0.992–6.628, $P = 0.046$). Furthermore, concomitant Hashimoto's thyroiditis and ETE were not more likely to show skip metastasis (P value > 0.05).

Multivariate Analysis

Furthermore, predictive factors were screened after the multivariate logical analysis. In current research, predictive factors, such as tumor diameter ≤ 10 mm (OR = 3.417, 95% CI 1.250–9.343, $P = 0.017$), unilaterality (OR = 4.562, CI 1.017–20.468, $P = 0.048$), microcalcification (OR = 2.927, CI 1.087–7.879, $P = 0.034$), and upper location of PTC (OR = 10.303, CI 2.290–46.353, $P = 0.002$) were identified as predictive factors for skip metastasis of LLNM in participants with PTC (Table 2, Figure 1). It is noted that BRAF^{V600E} mutation (P value > 0.05) was not the predictive factor after the multivariate logical analysis.

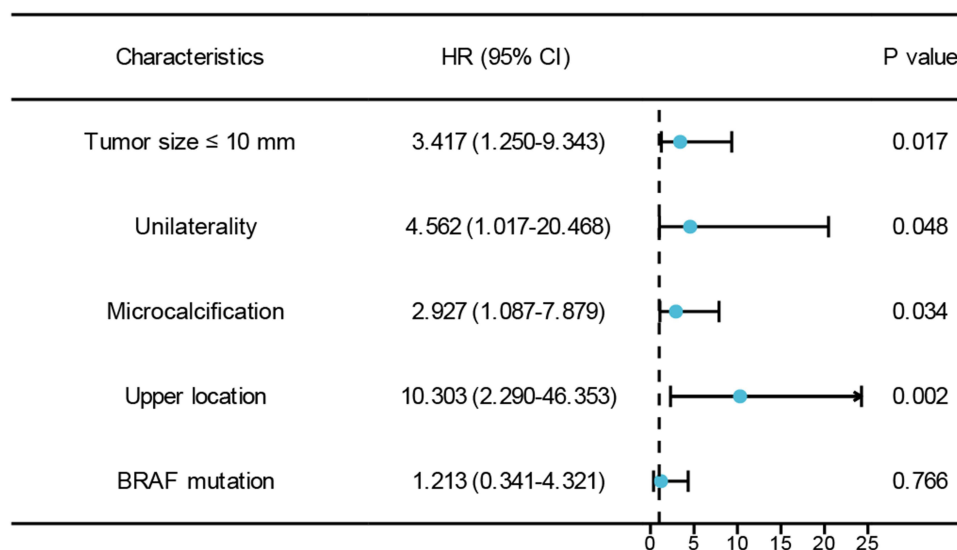


Figure 1 Forest plot of the risk factors of skip metastasis in PTC patients.

Table 3 ROC Analysis of the Independent Factors and Equation for Predicting Skip Metastasis of LLNM in PTC Patients

	Az	95% CI	Cutoff Value	Sensitivity	Specificity
Overall (N=228)					
Tumor size≤10 mm	0.678	0.571–0.785	Tumor size≤10 mm	0.704	0.652
Unilaterality	0.602	0.491–0.713	Unilaterality	0.667	0.537
Microcalcification	0.638	0.526–0.750	Microcalcification	0.630	0.647
Upper location	0.696	0.593–0.800	Upper location	0.741	0.652
Predictive equation	0.783	0.682–0.885	0.159	0.704	0.791

ROC Curve

ROC analysis was performed for this prediction model, and the diagnostic value of these predictive factors was discriminative with areas under the curves of 0.678 (95% CI: 0.571–0.785), 0.602 (0.491–0.713), 0.638 (0.526–0.750), and 0.696 (0.593–0.800), respectively. In addition, their sensitivity and specificity were 70.4% and 65.2%, 66.7% and 53.7%, 63.0% and 64.7%, and 74.1% and 65.2%, respectively (Table 3, Figure 2a).

Predictive Model

Using the coefficients required from the multivariate analysis, we derived the following prediction equation for skip metastasis where the categorical variables were coded as “1” if present and “0” if absent. The multivariate logistic regression equation was performed with above risk factors:

$P = 1 / 1 + \exp[-3.536 + 1.229 \times (\text{if tumor nodule} \leq 10\text{mm}) + 1.518 \times (\text{if unilaterality nodule}) + 1.074 \times (\text{if microcalcification in nodule}) + 2.332 \times (\text{if nodule in upper location})]$, where P means the chance of a positive skip metastasis (Figure 2b). The value of 0.159 was selected as the optimal cut-off point, meaning that the PTC patients with a predictive rate higher than 0.159 were prone to have skip metastases in PTC patients, which can provide guidance for these PTC patients to perform LLND. The predictive model demonstrated a satisfactory predictability of skip metastasis (AUC = 0.783, 95% CI 0.682–0.885) with the sensitivity and specificity were 70.4% and 79.1%, respectively. The 0.783 value of AUC in our predictive model was higher than other four independent risk factors, indicating the great diagnostic

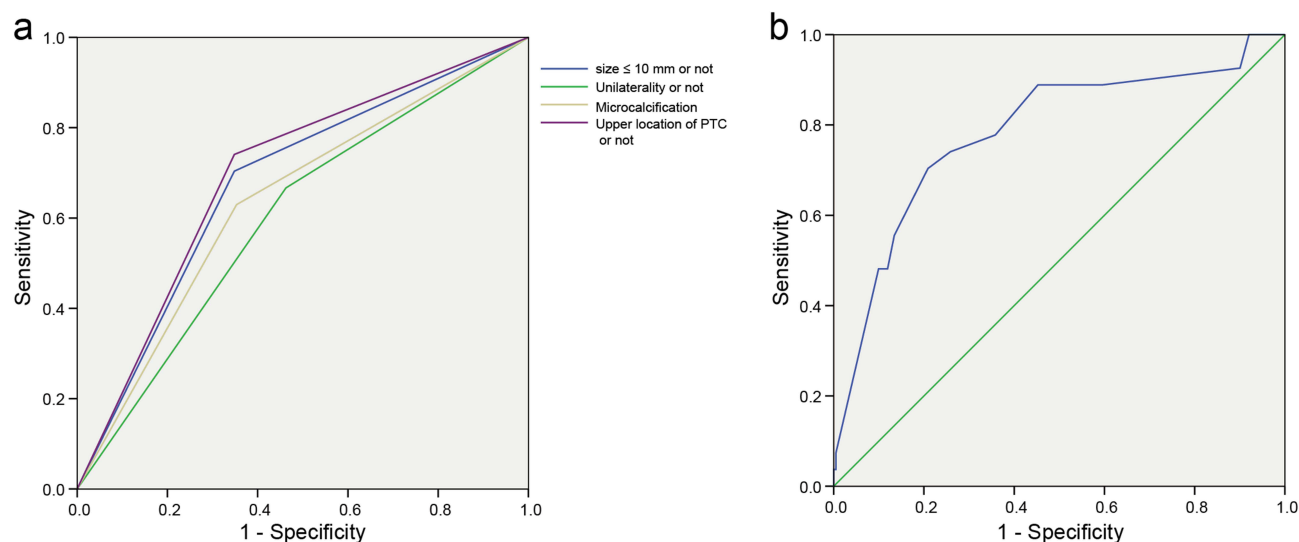


Figure 2 Receiver operating characteristic (ROC) curves of (a) tumor size ≤ 10 mm (area under the ROC curve [AUROC] = 0.678), unilaterality (AUROC = 0.602), microcalcification (AUROC = 0.638), and upper location of PTC (AUROC = 0.696), respectively. (b) Equation (AUROC = 0.783) for the prediction of skip metastasis.

efficiency with a value of 1.0 representing a perfect test. The larger the area of AUC is, the higher the predictive accuracy.

Discussion

In the present research, tumor size ≤ 10 mm, unilaterality, microcalcification, and upper tumor location can increase the risk of skip metastasis in PTC patients, which provides the useful information for clinicians to select prophylactic LLN dissection before the operation, thereby reducing the possibility of recurrence of PTC and avoiding the secondary operation for patients.

US-guided fine needle aspiration (FNA) was often conducted to evaluate the malignant risk of PTC. According to the Bethesda system, the results of a cytological biopsy can be divided into the following six categories: I (non-diagnostic or unsatisfactory), II (benign), III (atypia of undetermined significance [AUS] or follicular lesion of undetermined significance [FUS]), IV (follicular neoplasm or suspicious for a follicular neoplasm), V (suspicious for malignancy), and VI (malignant).^{27,28} Despite the PTC is one of the indolent carcinomas with low mortality rate, the regional recurrence and distant metastasis may happen in approximately 20–30% of PTC patients, which are dominantly related to the metastatic cervical lymph nodes.^{29–31} Total thyroidectomy (TT) and subtotal thyroidectomy (STT) are the two mainstream surgical methods. One previous reported that TT could be safely performed in PTC patients without increasing risk of early complication.³² Preventive LLND is not recommended when the CLNM is not found in the intraoperation unless the preoperative examinations visualize the occurrence of LLNM. However, it is unfortunate that the preoperative LLNM visualization is reported to be a high false-negative rate, and the diagnostic accuracy was largely based on the experience of the operator,^{12,33} which could increase the possibility of local and regional recurrence and distant metastasis, affecting the disease-free survival rate of PTC patients. The evaluation of PTC invasiveness from US features, biomarker and clinicopathology of PTC may provide the basis for the prediction of LLNM and the selection of surgical methods. These skip metastases, regarded as LLNM without the involving the CLNM, could contribute to incomplete lymph node dissection in the intraoperation, which may consequently have an adverse effect on the prognosis of patients with PTC. Hence, it is critical to carry out a precisely preoperative estimation of skip metastasis in PTC patients.

The skip metastasis rate of LLNM in this cohort was 11.8% (27/228), which was in the range of 0.6% to 37.5% according to the previous reports.^{34–39} The skip metastasis rate in the latest study with a large sample was 15.4% (41/267), which was very close to our results.⁸ These following clinicopathologic and ultrasonic features, including tumor size ≤ 10 mm, unilaterality, microcalcification, and upper tumor location were independent predictive factors for the progression of skip metastasis in PTC patients. Other characteristics were not significantly correlated with skip metastasis in patients with PTC.

The size of primary tumor is one of important variables evaluated for the biological characteristics, because the diameter of target PTC can be easily required through preoperative US detection.⁴⁰ In our research, the occurrence of skip metastasis was more frequently in tumor size ≤ 10 mm than in >10 mm PTC. One literature has covered that the occurrence of skip metastasis was more common in smaller PTC patients,^{41,42} especially those with the diameter of primary tumor <5 mm.³⁵ Moreover, the tumor location in the upper pole is also predictive factor of skip metastasis in PTC, which was in agreement with other previous reports.^{12,19,43} This phenomenon can be explained that the lymphatic drainage system of the upper pole of the thyroid lobe exhibits a discernible distinction from that of the remaining portion of the thyroid lobe. The superior thyroid artery, through which lymphatic flow occurs, is more prone to transporting tumor cells from the upper region to the lateral lymph nodes. Furthermore, we also found unilaterality PTC could increase the risk of skip metastasis in our study, which was consistent with the previous finding.⁸ The patients harboring bilateral PTCs have a higher risk of metastatic central lymph nodes as compared to the patients with unilaterality. Unilaterality PTC is obviously correlated with an improved occurrence of skip metastasis. Furthermore, microcalcification is a typical US sign of calcium salt deposition caused by the hyperplasia fibers and blood vessels, which suggests the fast growth and development of malignant tumors.⁴⁴ Thus, the lymph nodes in lateral scope should be examined more carefully when the microcalcification is found in PTC. In addition, oxidative stress has been indicated as an important risk factor of PTC, is closely involved in angiogenesis and aggressiveness among PTC.⁴⁵ Oxidative stress stimulates the

secretion of angiogenic modulators in PTC cells via hypoxia-dependent and -independent pathways, and several oxidative stress-related biomarkers could be potentially considered as PTC angioinvasion screening tools.⁴⁵ Previous finding reported that angioinvasion was independent risk factors for cervical LNM in PTC patients.⁴⁶ However, PTC angioinvasion was not considered in the current study, which was resulted from the small samples. Our group will put great effort to investigate the relationship between angioinvasion screen and skip metastasis of LLNM in the futural research.

Ultimately, a predictive model was established according to these above independent factors of skip metastasis. The OR value of tumor size ≤ 10 mm, unilaterality, microcalcification, and upper location of PTC was 3.417, 4.562, 2.927, and 10.303, respectively. The predictive model exhibited a satisfactory predictability of skip metastasis (AUC = 0.783, 95% CI 0.682–0.885) with the sensitivity and specificity were 70.4% and 79.1%, respectively. Its sensitivity for predicting skip metastasis in patients with PTC is superior to that of traditional ultrasound or CT alone. When the predicted rate is more than 0.159, the existence of skip metastasis of LLND should be considered. Compared with previous research, these four predictive factors can be easily obtained from preoperative US examination, which is expected to provide useful information to evaluate the intraoperative window before the surgical operation.

It is undenied that there are some drawbacks in our research. Firstly, our research was retrospective research, and thus, selection bias was not avoidable in our study. Secondly, the disease-specific survival, locoregional recurrence, and distant metastasis of PTC were not investigated because of the short follow-up time. Thirdly, eastographic and contrast evaluation of PTC features were not studied in our study. Hence, the prospective multicenter and multimode research are warranted to investigate the predictive factors of skip metastasis in patients with PTC in the future.

Conclusion

In conclusion, our study has identified specific factors associated with skip metastasis in PTC patients, including tumor size ≤ 10 mm, unilaterality, microcalcification, and upper location of PTC. The predictive model was established to help surgeons determine which patients accept LLND before the surgery, which can predict skip metastasis in PTC patients without invasive procedures, reducing patients' pain and promoting the rational use of medical resources. The LLND should be recommend for these PTC patients when the predictive rate exceeds 0.159. Our study is useful to assist in identifying PTC patients who need the LLND and guide the precise medicine for individual PTC patients. Large-scale and multicenter researches with long-term follow-ups are required to verify our predictive model for skip metastasis in PTC.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

Our research design followed the international regulations based on the Declaration of Helsinki. This research was approved by the Ethical Committee of the Affiliated Hospital of Jiangsu University (SWYXLL20190225-2), and written informed consent was obtained from the participants prior to study commencement.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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