Brazilian Journal of
OTORHINOLARYNGOLOGY
www.bjorl.org

ORIGINAL ARTICLE

Comprehensive analysis of clinicopathologic and sonographic features in thyroid cancer with skip lymph node metastasis: establish and assessment of a prediction nomogram

Liang Jiwang [a,*,1], Bai Jinghui [b,1], Fang Fengqin [a], Yu Tao [c], Zhao Yuejiao [a,*]

[a] *Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, Department of Head and Neck Surgery, Liaoning Province, Shenyang, China*
[b] *Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, Department of General Medicine, Liaoning Province, Shenyang, China*
[c] *Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, Department of Medical Imaging, Liaoning Province, Shenyang, China*

Received 3 October 2022; accepted 23 July 2023
Available online 3 August 2023

HIGHLIGHTS

- A few studies have focused on skip metastasis, and the clinical and pathological risk factors remain uncertain. Some researchers have also proposed different models for predicting its occurrence, but their models were only based on the clinicopathologic characteristics, and none of them included US features. In this study, we retrospectively examined the incidence and related clinicopathologic and US characteristics of skip metastasis in PTC and papillary thyroid microcarcinoma.
- We established a nomogram for predicting the possibility of skip metastasis according to the clinicopathological and US features.
- The number of patients in this study is 1037, this sample is relatively larger than other study. The results of our study might be less bias.

KEYWORDS
Papillary thyroid carcinoma;
Skip metastasis;
Ultrasonography;
Nomogram

Abstract Lateral Lymph Node Metastasis (LLNM) is common in Papillary Thyroid Carcinoma (PTC) and is associated with a poor prognosis. LLNM without central lymph node metastasis as skip metastasis is not common. We aimed to investigate clinicopathologic and sonographic risk factors for skip metastasis in PTC patients, and to establish a nomogram for predicting the possibility of skip metastasis in order to determine the therapeutic strategy. We retrospectively reviewed the data of 1037 PTC patients who underwent surgery from 2016 to 2020 at a single institution. Univariate and multivariate analyses were used to identify the clinicopathologic and preoperative sonographic risk factors of skip metastasis. A nomogram including the risk

* Corresponding author.
E-mails: liangjiwang1985@163.com (L. Jiwang), 13352468831@qq.com (Z. Yuejiao).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.bjorl.2023.101301

factors for predicting skip metastasis was further developed and validated. The incidence of skip metastasis was 10.7%. The univariate and multivariate analyses suggested that gender (p = 0.001), tumor location (p = 0.000), extrathyroidal extension (p = 0.000), and calcification (p = 0.000) were independent risk factors. For papillary thyroid microcarcinoma, tumor location (p = 0.000) and calcification (p = 0.001) were independent risk factors. A nomogram according to the clinicopathologic and sonographic predictors was developed. The receiver operating characteristic curve indicated that AUC was 0.824 and had an excellent consistency. The calibration plot analysis showed a good performance and clinical utility of the model. Decision curve analysis revealed it was clinically useful. A nomogram for predicting the probability of skip metastasis was developed, which exhibited a favorable predictive value and consistency. For the female PTC patient, tumor located at the upper pole is more likely to have skip metastasis. Surgeons and sonographers should pay close attention to the patients who have the risk factors.

Evidence level: This article's evidence level is 3. Level 3 evidence is derived from non-randomized, controlled clinical trials. In this study, patients who receive an intervention are compared to a control group. Authors may detect a statistically significant and clinically relevant outcome.

Introduction

Papillary Thyroid Carcinoma (PTC) has become one of the fastest-growing tumors in the world.[1] It has an excellent prognosis, but a subgroup of PTC is aggressive and shows easier recurrence or distant metastasis in patients with lymph node metastasis (LNM). Previous studies reported that approximately 25%–64% of patients developed Central Lymph Node Metastasis (CLNM),[2,3] and Lateral Lymph Node Metastasis (LLNM) occurred in 17.3%–60%.[4,5] It has demonstrated that LNM occurs in a sequential pattern. LNM shows extension first to the central area then to the ipsilateral lateral cervical lymph node, and this is followed by extension to the contralateral lateral lymph node. However, some patients develop LLNM without CLNM in clinical practice, which has been referred to as ''skip metastasis''. This phenomenon is uncommon. The frequency of skip metastasis in PTC varies considerably, ranging from 6.5%–27.5%.[6–10]

For cN1 patients, Lateral Lymph Node Dissection (LLND) is proposed in most medical institutions. Those low-risk patients who have no clinical or radiographic evidence of invasion or metastasis, prophylactic LLND will undoubtedly increase the probability of complications. This is not recommended by the American Thyroid Association (ATA) management guideline.[5] Therefore, it makes the meticulous preoperative examination more crucial in LLNM management. Ultrasound (US) is the primary examination method, but sometimes, abnormal lymph node may not be found when it is microcalcification or overlaid by thyroid. For the lymph nodes without typical image features, US is considered insufficient. Although more advanced diagnostic tools are now used, preoperative diagnosis of LLNM, especially skip metastasis, is still a challenge for clinicians.

Currently, a few studies have focused on skip metastasis, and investigated the risk factors.[7–12] Some researchers also proposed different models for predicting its occurrence,[7,13,14] but no definite conclusion has been drawn from these works. It should be noted that these models were only based on the clinicopathologic characteristics, and none of them included US features. In this study, we retrospectively examined the clinicopathologic and US characteristics of skip metastasis in PTC, attempting to reveal the independent predictors. We established a nomogram for predicting the possibility of skip metastasis according to these features.

Methods

This is a retrospective study. The present study was accordance with the Declaration of Helsinki and was approved by ethical committees of our hospital, and informed consent was obtained from each patient (approval nº 20181207). 2248 consecutive patients who underwent thyroid surgical treatment in our institution Between July 2016 and December 2020 were retrospectively analyzed. The inclusion criteria were as follow: 1) Patients who underwent thyroidectomy together with central and when necessary, therapeutic lateral neck dissection; 2) PTC had been confirmed by histopathological examination; 3) Patients without previous history of radiation and other head and neck malignant tumors. After the inclusion criteria, 1037 patients were included. Clinicopathological variables such as age at diagnosis, gender, primary tumor size, location, Hashimoto Thyroiditis (HT), multifocality, bilaterality, Extrathyroidal Extension (ETE), capsule invasion, type of surgery, CLNM and LLNM were collected. Tumor location is categorized as upper, middle, and lower third of thyroid. Because there is no clear anatomical division or guideline, the thyroid gland is bisected into three equal volumes (upper, middle, and lower pole) according to the consensus of most medical centers. Multifocality is defined as two or more tumors in the thyroid. Bilaterality means presence of tumors in both thyroid lobes. Capsule invasion means tumor lesion invading into the thyroid capsule, but not penetrating it. In contrast,

ETE is defined as tumor penetrating through the capsule and invading skeletal muscle tissue or perithyroidal soft tissue.

In our department, preoperative evaluation included careful history, physical examination, thyroid function assessment, and US of the neck. All patients underwent a preoperative examination with a high-resolution US equipped with a 7–12 MHz linear probe. All neck US examinations were performed by sonographers with more than 5 years of experience in thyroid imaging. US features of tumor included nodule number, margin, shape, internal content, echogenicity, calcification, Anteroposterior to Transverse ratio (A/T), and blood flow. Clinical positive LLNM was suggested if the following features were noted on US: absence of an echogenic hilum, round shape, microcalcification, peripheral blood flow, or cystic changes. Whether to perform LLND was determined based on preoperative imaging examination.

The number of metastatic lymph nodes or lymph nodes dissected was expressed as mean ± standard deviation. Univariate analyses were performed for the association between skip metastases and clinicopathological factors using the Pearson's chi-square test or and Fisher's exact test. All of the variables with $p < 0.05$ were included in the multivariate analysis to assess the independent predictive factors using a Cox regression analysis. The findings were considered as Odds Ratio (OR) having 95% Confidence Interval (95% CI) and as *p*-value. Each *p*-value was two-sided. The diagnostic efficacy was evaluated using the Receiver Operating Characteristic (ROC) curve. The calibration curve was used to determine the prediction compliance. The clinical application value of diagnostic model was evaluated by the Decision Curve Analysis (DCA). A $p < 0.05$ represented a statistically significant difference. All statistical analyses were performed using the SPSS 17.0 statistical package (SPSS, Inc., Chicago, IL, USA), and R language software and the rms package.

Results

There were 216 males and 821 females (ratio 1:3.8), and 806 patients aged <55 years and 231 patients aged ≥55 years. The mean maximum tumor size was 1.27 ± 0.92 cm. 565 patients had a tumor smaller than 1.0 cm. Tumor location was divided into upper third ($n = 252$), others ($n = 785$). Among all patients, 131 patients exhibited ETE, 317 patients presented capsule invasion. Multifocal tumors were observed in 255 patients. Bilaterality was detected in 208 patients, and HT was found in 275 patients. CLNM was identified in 362 patients, and LLNM was identified in 180 patients, both CLNM and LLNM was 476 patients. The mean number of CLND (central lymph node dissection) and LLND was 3.76 ± 2.99 and 15.71 ± 8.44, respectively. The mean number of CLNM was 2.68 ± 1.39, and that of LLNM was 4.83 ± 3.15 (Table 1). The rate of skip metastasis was 10.7% ($n = 111$). The mean number of CLND and LLND in patients with skip metastasis was 3.22 ± 2.72 and 14.85 ± 8.78, respectively. As showed in Table 2, triple level metastases ($n = 45$) were the most common pattern, followed by single level metastasis ($n = 24$), double level metastases ($n = 11$) and four level metastases ($n = 8$). In addition, levels III and IV were the most involved sites, whether in single level metastasis or double level metastases.

Table 1 Patients demographics and clinicopathological characteristics.

Variables	Total
Gender	
Male	216 (20.8%)
Female	821 (79.2%)
Age (years)	45.05 ± 11.93
Tumor size (cm)	
≤1	565 (54.5%)
1–2	308 (29.7%)
≥2	164 (15.8%)
Tumor location	
Upper third	252 (24.3%)
Other	785 (75.7%)
Multifocality	255 (24.6%)
Bilaterality	208 (20.1%)
Capsule invasion	317 (30.6%)
ETE	131 (12.6%)
HT	275(26.5%)
CLNM	362 (34.9%)
LLNM	180 (17.4%)
Skip metastasis	111 (10.7%)
Preoperative distant metastasis	5 (0.5%)
CLND number	3.76 ± 2.99
CLNM number	2.68 ± 1.39
LLND number	15.71 ± 8.44
LLNM number	4.83 ± 3.15

Table 2 Distribution of skip metastasis in 111 PTC patients.

Distribution	Number of patients
Single level ($n = 24$)	
Level II	2
Level III	12
Level IV	10
Level V	0
Double levels ($n = 11$)	
Level II + III	4
Level III + IV	6
Level IV + V	1
Triple levels ($n = 45$)	
Level III + IV + V	43
Level II + III + IV	2
Four levels ($n = 8$)	
Level II + III + IV + V	8

The clinicopathological features between two groups (presence versus absence of skip metastases) were compared to determine the clinical features related to skip metastases. The risk factors of PTC with skip metastasis are shown in Table 3. We found that gender, age, tumor size, tumor location, multifocality, bilaterality, capsule invasion, and ETE were significantly associated with skip metastasis. Multivariate analysis revealed that gender, tumor location, and ETE were independent factors. For the Papillary Thyroid Microcarcinoma (PTMC) patients, multivariate analysis

Table 3 Univariate and multivariate analysis results of clinicopathologic characteristics for skip metastasis in PTC patients.

Variables	Univariate analysis			Multivariate analysis		
	Skip metastasis (+)	Skip metastasis (−)	*p*	OR	95% CI	*p*
Gender			0.003	0.463	0.292–0.734	0.001
Male	36	180				
Female	75	746				
Age (years)			0.016	0.664	0.417–1.058	0.085
<55	76	730				
≥55	35	196				
Tumor size (cm)			0.000	0.679	0.412–1.119	0.129
≤1	33	532				
>1	78	394				
Tumor location			0.000	1.546	1.343–1.779	0.000
Upper third	43	209				
Mid third	23	479				
Lower third	11	129				
Isthmus	1	35				
Multicentric	28	55				
Whole	5	19				
Multifocality			0.000	2.365	0.938–5.963	0.068
Present	59	196				
Absent	52	730				
Bilaterality			0.000	1.627	0.632–4.191	0.313
Present	53	155				
Absent	58	771				
Capsule invasion			0.006	0.640	0.356–1.149	0.135
Present	47	270				
Absent	64	656				
ETE			0.000	3.291	1.732–6.254	0.000
Present	37	94				
Absent	74	832				
HT			0.14			
Present	36	239				
Absent	75	687				
CLND number	3.22 ± 2.72	3.81 ± 3.01	0.087			
LLND number	14.85 ± 8.78	16.53 ± 8.03	0.441			
LLNM number	4.34 ± 2.82	5.61 ± 3.47	0.191			

showed that only tumor location was an independent factor (Table 4). Preoperative US characteristics were compared with and without skip metastasis, as presented in Table 5. Univariate analysis showed that statistical differences internal structure, calcification, and blood flow between the two groups. Multivariate analysis revealed that calcification was found to be an independent risk factor in PTC. For the PTMC patients, calcification was the independent factor (Table 6).

Then, we constructed a predictive nomogram which incorporated the significant risk factors (Fig. 1). The nomogram integrated clinicopathological and US factors (gender, tumor location, ETE, and calcification) to assist in preoperative predicting skip metastasis. Each level within variables was assigned a score according to the point scale. By adding the total score and locating it on the total point scale, a corresponding probability of skip metastasis of each individual was determined. The predictive value was verified by ROC curves (AUC = 0.824; 95% CI 0.785–0.863) (Fig. 2). The nomogram exhibited an excellent consistency, which was evaluated by the Calibration curve (Fig. 3). The DCA demonstrated that predicting skip metastasis applying this model would be better than having all patients or none patients with a range of the threshold probability ranged from 0.007 to 0.443 (Fig. 4).

Discussion

PTC patients have high morbidity and a low mortality. They often have LNM, which is associated with locoregional recurrence. Usually, LNM has no significant effect on patient's outcome. However, several recent studies suggested it does have impact on survival in high-risk patients in some degree.[15,16] For example, Kim et al. reported stage II patients with lymph node risk (largest lymph node size >3 cm or LLNM ratio >0.3) had a much higher cancer-specific mortality rate than those in the same stage without lymph node risk (20.9% vs. 3.2%).[17] There is a consensus that LLNM is a significant risk factor for lower survival rate, so LLND is considered an important part of PTC treatment. Preoperative

Table 4 Univariate and multivariate analysis results of clinicopathologic characteristics for skip metastasis in PTMC patients.

Variables	Univariate analysis			Multivariate analysis		
	Skip metastasis (+)	Skip metastasis (−)	*p*	OR	95%CI	*p*
Gender			0.066			
Male	11	99				
Female	22	433				
Age (years)			1.0			
<55	27	429				
≥55	6	103				
Tumor location			0.000	1.689	1.294–2.204	0.000
Upper third	11	121				
Mid third	10	301				
Lower third	4	75				
Isthmus	0	15				
Multicentric	8	17				
Whole	0	3				
Multifocality			0.000	2.033	0.979–4.223	0.057
Present	17	87				
Absent	16	445				
Bilaterality			0.000	3.683	0.990–13.696	0.052
Present	14	65				
Absent	19	467				
Capsule invasion			0.818			
Present	5	100				
Absent	28	432				
ETE			0.574			
Present	1	13				
Absent	32	519				
HT			0.017	1.479	0.384–5.695	0.570
Present	16	149				
Absent	17	383				
CLND number	3.44 ± 3.10	3.61 ± 2.87	0.443			
LLND number	13.90 ± 9.47	15.82 ± 7.84	0.309			
LLNM number	3.21 ± 2.13	4.50 ± 3.09	0.167			

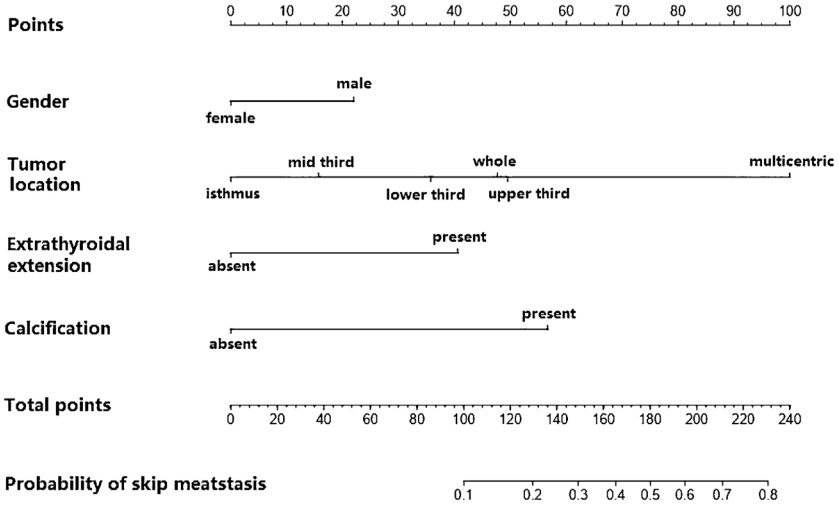

Figure 1 Nomogram for predicting skip metastasis in PTC patients.

Table 5 Univariate and multivariate analysis results of ultrasonographic characteristics for skip metastasis in PTC patients.

Variables	Univariate analysis			Multivariate analysis		
	Skip metastasis (+)	Skip metastasis (−)	*p*	OR	95%CI	*p*
Number of nodules			0.111			
≤1	17	205				
>1	94	721				
Shape			1.000			
Regular	11	96				
Irregular	100	830				
Margin			1.000			
Smooth	13	108				
Ill-defined	98	818				
Echogenicity			0.132			
Markedly hypoechoic	1	37				
Hypoechoic	108	853				
Isoechoic/ hyperechoic	2	36				
Internal structure			0.006	3.608	0.947–13.749	0.06
Solid	109	893				
Cystic	2	2				
Mixed	0	31				
Calcification			0.000	6.475	3.075–13.635	0.000
Present	103	561				
Absent	8	365				
A/T			0.538			
<1	26	192				
≥1	85	734				
Blood flow			0.000	1.488	0.971–2.280	0.068
No	11	97				
Little	70	754				
Rich	30	75				

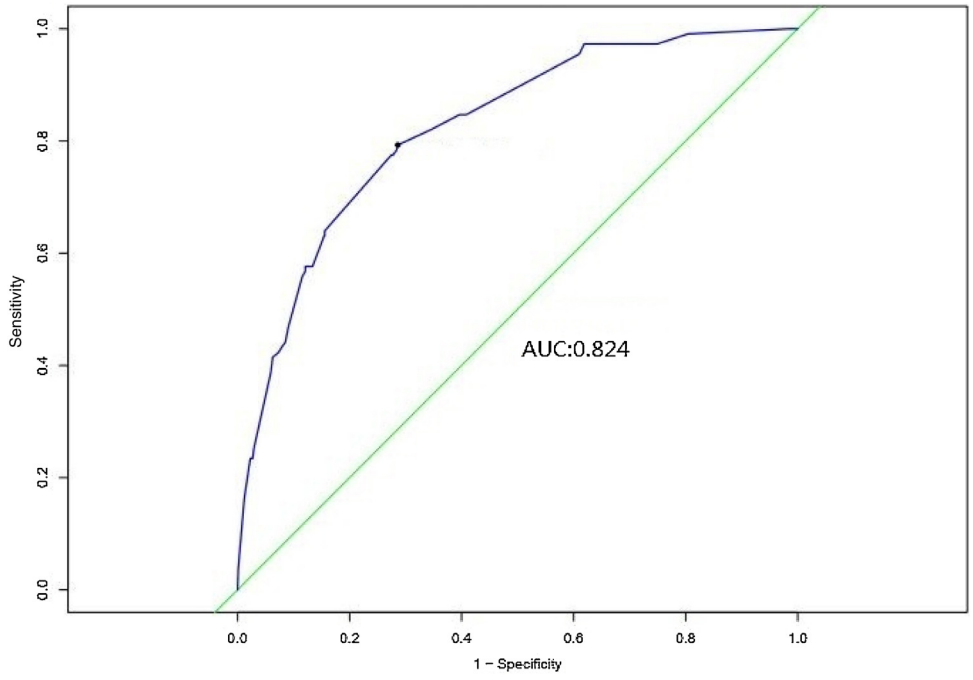

Figure 2 ROC curve analysis to predict skip metastasis in PTC patients.

Table 6 Univariate and multivariate analysis results of ultrasonographic characteristics for skip metastasis in PTMC patients.

Variables	Univariate analysis			Multivariate analysis		
	Skip metastasis (+)	Skip metastasis (−)	*p*	OR	95%CI	*p*
Number of nodules			0.511			
≤1	5	113				
>1	28	419				
Shape			0.231			
Regular	5	49				
Irregular	28	483				
Margin			0.364			
Smooth	5	52				
Ill-defined	28	480				
Echogenicity			0.141			
Markedly hypoechoic	0	33				
Hypoechoic	32	495				
Isoechoic/hyperechoic	1	4				
Internal structure			0.000	0.126	0.009–1.683	0.117
Solid	32	529				
Cystic	0	0				
Mixed	1	3				
Calcification			0.000	5.384	2.011–14.410	0.001
Present	27	263				
Absent	6	269				
A/T			0.098			
<1	4	135				
≥1	29	397				
Blood flow			0.000	0.741	0.341–1.607	0.448
No	9	67				
Little	19	448				
Rich	5	17				

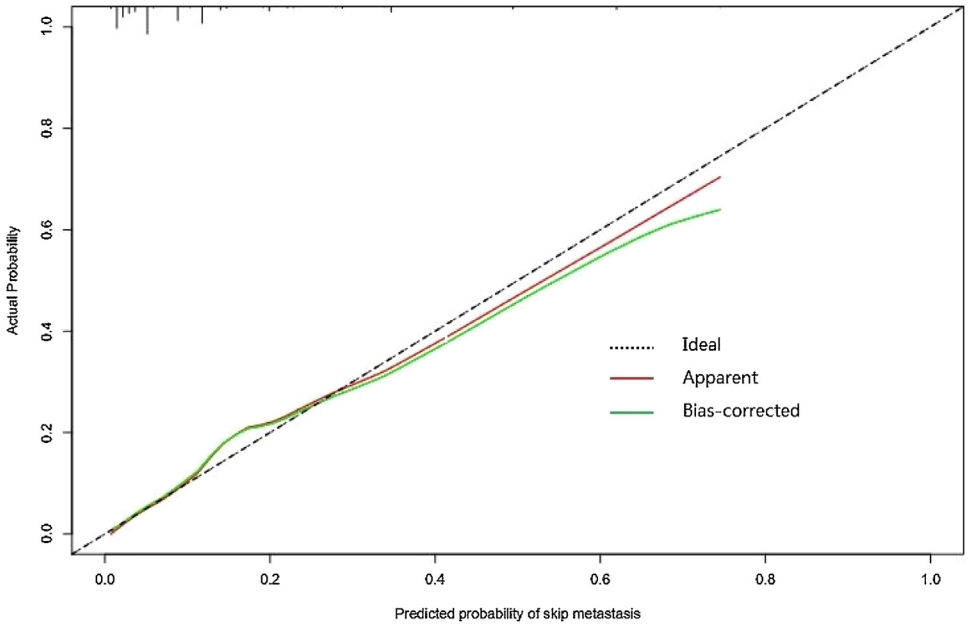

Figure 3 Calibration curve of the nomogram for predicting skip metastasis in PTC patients.

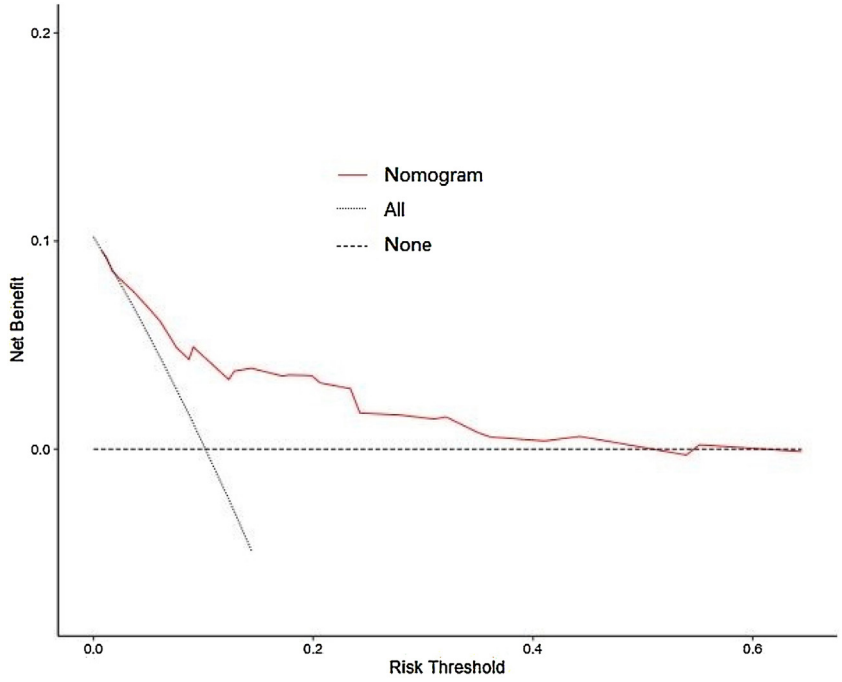

Figure 4 Decision curve analysis for skip metastasis in PTC patient.

predicting the risk factor for LLNM is essential in forming appropriate treatment protocols.

Compared with the general patterns of thyroid lymphatic drainage, skip metastasis is a specific but rare type. It is found to be associated with a good prognosis in some malignancies (non-small-cell lung and colorectal cancer).[18,19] On the contrary, it has a bad influence on survival in breast cancer.[20] The cause of skip metastasis in PTC is still unknown. Several hypotheses were proposed,[11,21] such as bypassing the normal anatomic lymphatic channels, previous surgical treatment altering the normal pathway of lymphatic drainage, or false-negative findings. Other authors considered it might be an unstable LNM phenomenon of PTC but was not due to limited or missed lymph node samples.[22] The patients who had reoperation and neck irradiation were excluded in this study. Considering the mean number of CLND was relatively adequate compared to previous studies ($n = 3.22$), we speculated the cause of skip metastasis might be in line with the first mechanism. The rate in this study was 10.7%, which could not be ignored in clinical practice. With respect to the distribution of LLNM in skip metastasis, level III is the most frequently metastatic site, followed by level IV, II, and V.[7,8,11] However, some authors reported the involvement of level II was commonly observed in patient with skip metastasis.[7,8] Our finding demonstrated that level III nodes were the most frequently involved nodes (10.8%), which was similar with previous studies.

Next, through the multivariate logistic regression analysis, we found gender, tumor location, and ETE were independent risk factors. Most published studies indicated that skip metastasis had a higher rate in female patients, but gender was not an independently predictive factor.[11–13,23] Different from those studies, our results revealed that female was a risk factor. The same result also appeared in another research.[10] It is generally accepted that tumor location in the upper pole is a predictor.[7,9,12,23] This correlation could be explained by the lymphatic drainage system. The tumor cells from the upper region are more likely than those from the lower region to be transported to the lateral lymph nodes by lymphatic flow along the superior pole vessels. Meanwhile, it can also explain LNM arising from tumor located in the upper portion are more frequent in level III than in the other levels. Interestingly, LLNMs arising from the upper third in patients with CLNM were more frequent in level II.[8] We speculated that the lymphatic drainage system in the upper pole might be different from that in other parts. At present, the relationship between tumor location and skip metastasis remains controversial. Besides, several studies have described gross ETE as a predictive factor for recurrence and poor outcome, independently affecting disease-free survival and disease-specific survival.[24,25] We found ETE was an independent predictor ($p = 0.000$). However, for capsule invasion, it was not an independent risk factor. According to our clinical observation and experience, no matter whether tumor invades outside of thyroid or not, the existence of close infiltration to the capsular can lead to high LLLN metastasis risk.

The number of CLNM is often used to predict whether metastasis occurred in clinical practice. As an important risk factor for LLNM, the number of CLNM is increasingly being included in risk stratification, with typical cutoff values of 2–3 and 5.[26–28] The number of CLND was regarded as an important independent factor for LLNM.[10] Some authors proposed to perform LLND when the number of CLNM was ≥ 2.[29] When the number of CLNM was ≥ 3, Cai et al. suggested it could be used as a quantitative index for predicting LLNM, and LLND should be recommended.[30] Our results exhibited that the number of CLND was smaller in the skip metastasis group (3.22 ± 2.72 vs. 3.81 ± 3.01). There was no significant difference between the two groups, and it was not an inde-

pendent factor. For skip metastasis, whether it has the same significance is unclear, and no definite conclusion has been drawn from published studies.[7,13,31]

Metastatic lymph node often manifests as hyperechoic mass or whole hyperechoic change, calcification, irregular margin, cystic change, and round shape.[32] Kwak et al. proposed several US characteristics, such as upper location, contact of 25% with the adjacent capsule, and calcification, were predictive factors for LLNM.[33] Zeng et al. in their study revealed that upper location, no well-defined margin, and calcification were independent predictors for LLNM.[34] Wang et al. reported that PTC with abutment/perimeter $\geq$1/4 and upper location were prone to skip metastasis.[35] Similar results were found in this study, however, only calcification was a predictive factor. Many studies have found that the presence of calcification was an independent factor for LLNM.[33,34,36] Currently, there is few research on preoperative US diagnosis of skip metastasis, and there is still a lack of studies to provide available evidence.

According to the previous investigations, PTMC was considered as a risk factor for skip metastasis.[7,9] Despite some authors demonstrated skip metastasis was more frequent in PTMC,[6,7,11] our results only showed a smaller proportion (29.7%). Tumor size was not identified as an independent risk factor in this study. This was not consistent with the previous results. However, we still advise that clinicians should carefully evaluate lateral lymph node status when tumor sizes $\leq$1 cm. Further, we also investigated risk factors in these PTMC patients. Our results suggested that only tumor location was an independent predictor factor.

Preoperative US examination has some limitations, such as variable sensitivities and the difficulty in detecting deep lymph nodes. In addition, sometimes, the detection rate is affected by the field and expertise of the examiners, and some sonographers might overlook ambiguous lymph nodes in the clinical practice. An accurate preoperative diagnosis could hardly be achieved every time even by experienced sonographers. Thus, in this study, we considered that clinicopathological and sonographic results should be correlated to prevent under diagnosis of skip metastasis. A new assessment method for predicting skip metastasis need to be proposed and would be helpful in selecting therapeutic strategy which might avoid overtreatment or a missed diagnosis of metastatic lymph nodes. Nomogram is the visualization of statistical model specifically developed to optimize individuals' predictive accuracy. Several current studies have developed different models for predicting skip metastasis in PTC, but they were only based on clinicopathologic features.[13,14] Meanwhile, the predictive factors included in these nomograms were also inconsistent across studies. To our knowledge, this is the first retrospective study to explore clinicopathologic and sonographic risk factors in PTC patients and develop a diagnostic model to predict skip metastasis. Our nomogram, which included gender, tumor location, ETT, and calcification, exhibited a good predictive value (AUC was 0.824). The calibration curve exhibited the nomogram had acceptable prediction accuracy. In addition, clinical DCA demonstrated that most PTC patients could benefit from the predictive model. Thus, utilization of this model could provide an individual risk assessment and avoid unnecessary invasive procedures.

There are also several limitations to our study. First, our research was a single-center retrospective study, and it subjected to the inherent limitations of such studies. Second, LLND was performed only when the suspected lateral lymph node was pathologically proven; thus, some micrometastases may be missed. Third, different surgeons participated in performing thyroidectomy and LND, and surgeon-specific factors might influence the outcomes in some degree. In addition, the evaluation of US imaging factors involved some subjectivity. Interobserver variability among the sonographers performing real-time US may have been a factor, and our results cannot be reproducible at other institutions. Finally, the validation of the nomograms might be biased by institutional diagnostic patterns, the reproducibility and robustness of our nomogram needed to be validated in a prospective, multicenter study with a larger dataset.

In the present study, the incidence of skip metastasis in PTC is 10.7%, and this is not negligible. Female, tumor location in the upper pole, ETE, and calcification are independent risk factors in patients with PTC. For PTMC, tumor location in the upper pole and calcification are predictive factors of skip metastasis. Based on the clinicopathologic and US factors, we successfully established a visualized nomogram model for predicting skip metastasis in PTC. Further research is necessary to help tailor individual surgical interventions for patients with PTC.

Funding

This work was supported by the Natural Science Foundation of Liaoning Province (2023-MS-059, no.20180530038).

Conflicts of interest

The authors declare no conflicts of interest.

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