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RESEARCH

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A risk stratification model based on ultrasound radiologic features for cervical metastatic lymph nodes in papillary thyroid cancer

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Abstract

Background Accurate preoperative evaluation for metastatic lesions is significant for PTC patients. However, the stratification systems revealed inconsistencies in the ultrasound (US) features of cervical metastatic lymph nodes (LNs). This study aimed to investigate and develop a risk stratification model based on US radiologic features for cervical metastatic lesions in PTC patients.

Methods This study retrospectively enrolled 1806 LNs from 1665 PTC patients who underwent US-guided fine-needle aspiration biopsy for cervical LNs from January 2010 to December 2022. Univariable and multivariable logistic regression analyses determined and developed the independent risk US features and a risk stratification model for cervical metastatic LNs. The performance of the risk stratification model was assessed and validated by the Korean Society of Thyroid Radiology and the European Thyroid Association.

Results Among the 1806 LNs, 1411 LNs were pathologically diagnosed with malignant. Multivariate analysis indicated that the absence of fatty hilum, cystic components, round shape (SD/LD $\geq$ 0.5), abundant vascularity, hyperechogenicity (including hyper and hypo-echogenicity, and hyper-echogenicity), and calcifications (include microcalcification, and macrocalcification) were independent risk US features associated with malignant LNs. A risk stratification model for cervical metastatic LNs was developed based on these suspicious US features and showed well-predicted performance (C-index 0.840; 95% CI: 0.840–0.923).

Conclusion Our study proposed a new risk stratification system based on US radiologic features to predict cervical metastatic lymph nodes in PTC patients. We identified several risk factors for lymph node (LN) metastasis from PTC including the absence of fatty hilum, cystic components, round shape (SD/LD $\geq$ 0.5), abnormal vascularity, hyper-echogenicity, hyper- and hypo-echogenicity, microcalcification, and macrocalcification. These features could serve as valuable indicators for surgeons to accurately assess the status of cervical LNs.

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Keywords Papillary thyroid carcinoma, Ultrasound, Lymph node, Risk stratification model

Background

With the increase and the improvement of detection methods, the detectable rate of thyroid cancer has increased rapidly and thyroid cancer has become one of the fastest-growing cancers [1, 2]. Papillary thyroid carcinoma (PTC) is the most common subtype of thyroid cancer [3, 4]. Despite PTC being regarded as an indolent tumor [5], a considerable portion of PTC is prone to early cervical lymph nodes (LNs) metastases (approximately 30–80%) [6, 7], which is an important factor affecting the prognosis of PTC patients. Adequate preoperative evaluation and tailoring of surgical resections for primary and metastatic lesions are the most important for PTC patients [8–10], and to minimize the possibility of metastatic lesions residual and recurrence [11].

High-resolution ultrasound (US) of the neck is a noninvasive imaging technique and has become the preferred method in the preoperative evaluation of cervical LNs in PTC patients [12, 13]. Although the validity of preoperative US in the diagnosis of cervical metastatic LNs in PTC patients has been verified, a considerable number of cases are still misdiagnosed or missed [14, 15]. On this basis, two risk stratification systems for cervical malignant LNs have been proposed by the Korean Society of Thyroid Radiology (KSThR) [16, 17] and European Thyroid Association (ETA) [18, 19] to guide management for imaging-detected LNs in PTC patients. However, these classifications have not been fully verified, and show differences partially in detail.

Hence, this study aimed to determine the risk of US features for cervical metastatic LNs and developed and validated a risk stratification model based on US radiologic features for cervical metastatic LNs in PTC patients.

Materials and methods

Patients and study design

This retrospective study collected electronic medical records of 1955 PTC patients who underwent ultrasound (US) guided FNA biopsy for neck lymph nodes (LNs) and radical neck LNs dissection (Level II-VI) from January 2010 to December 2022 at the Xiangya Hospital, Central South University. This study followed the Declaration of Helsinki, and approved by the Ethics Review Committee of Xiangya Hospital, Central South University (20211245). The informed consent was waived because of the retrospective and anonymous nature of the study.

We conducted a comprehensive review of medical records to extract relevant data, including clinical characteristics such as sex, age at diagnosis, thyroid hormone levels, ultrasonographic features of lymph nodes, and tumor pathological characteristics. 331 patients were excluded for the following reasons: 161 patients due to incomplete clinical information, 135 patients with a history of neck surgery, and 30 patients combined with other head and neck malignancies. Finally, a total of 1665 PTC patients with 1806 diagnostic LNs were enrolled in this study.

Evaluation of ultrasonography features

All patients underwent high-resolution ultrasound of the neck imaging before surgery. Ultrasound images were generated utilizing a diverse array of equipment from 11 distinguished manufacturers with a 5–15 MHz linear high-frequency probe, including Mindray and SonoScape from Shenzhen, China; Vinno from Suzhou, China; Hitachi and Canon from Tokyo, Japan; GE Healthcare from Chicago, Illinois, USA; Philips from Amsterdam, Netherlands; Siemens from Munich, Germany; Esaote from Genoa, Italy; Aloka from Wallingford, Connecticut, USA; and Supersonic from Aix-en-Provence, France. The ultrasonographic features of the evaluated lymph nodes (LNs) are as follows:

Echogenicity

Lymph nodes are classified based on echogenicity into the following categories: anechoic, hypo-echogenicity, iso-echogenicity, hyper-echogenicity, and a combination of hyper- and hypo-echogenicity, with the anterior neck muscles serving as the reference standard. In this study, “hyper-echoic” refers to LNs exhibiting a uniformly hyperechoic appearance. The term “hyper- and hypo-echoic” indicates a non-uniform echo pattern, characterized by a combination of both hyperechoic and hypoechoic features. Additionally, both “hyperechoic” and the “combination of hyperechoic and hypoechoic” patterns are classified as hyperechoic.

Calcifications

LNs are categorized based on the presence of spot-like strong echoes in the ultrasound images into three types: absent calcifications, microcalcifications, and macrocalcifications.

Fatty hilum

LNs are classified based on the presence or absence of a fatty hilum in the ultrasound images.

Cystic components

LNs are classified as either solid or cystic based on the presence of echoless regions observed in the ultrasound images.

Longitudinal-to-transverse ratio

The shape of LNs is determined based on the longitudinal-to-transverse ratio (short axis/long axis) in the transverse plane of the ultrasound image. LNs are classified as flattened (short/long axis < 0.5) or rounded (short/long axis ≥ 0.5).

Vascularity

Vascular patterns are categorized into three types using color Doppler images: none, hilar pattern, and peripheral or diffuse pattern. The peripheral or diffuse pattern is considered indicative of abnormal vascularity.

Additionally, ultrasound images are evaluated to determine whether the lymph nodes have an irregular shape or indistinct margins.

Fine-needle aspiration (FNA) biopsy cytology and histopathological analysis serve as the benchmark for assessing lymph node metastasis. The diagnostic accuracy of our ultrasound examinations is determined by the percentage of cases in which the US findings regarding LN metastasis align with these established correct results.

Table 1 Comparison of demographic and clinicopathologic characteristics among benign and malignant lymph nodes in PTC patients

Characteristic	No. of (%)		*P* value[a]
	Benign	Malignant	
Clinical Characteristic			
No. of patients	373 (100.0%)	1292 (100.0%)	
Sex			
Male	102 (27.3%)	440 (34.1%)	**0.015**
Female	271 (72.7%)	852 (65.9%)	
Age, year			
Median (IQR)	43 (33–52)	37 (30–47)	**< 0.001[b]**
< 55 (year)	318 (85.3%)	1155 (89.4%)	**0.027**
≥ 55 (year)	55 (14.7%)	137 (10.6%)	
Hashimoto's thyroiditis	167 (44.8%)	530 (41.0%)	0.196
TSH (M ± SD, uIU/ml)	2.67 ± 5.50	2.81 ± 5.02	0.666[c]
Pathological Characteristic			
No. of diagnostic lymph nodes	394 (100.0%)	1411 (100.0%)	
Tumor size, mm			
Median (IQR)	11 (8–16)	17 (11–25)	**< 0.001[b]**
≤ 10 (mm)	195 (49.5%)	292 (20.7%)	**< 0.001**
> 10 (mm)	199 (50.5%)	1119 (79.3%)	
Multifocality	52 (13.2%)	271 (19.2%)	**0.006**
Bilateral tumor	104 (26.4%)	544 (38.6%)	**< 0.001**
Capsular invasion	174 (44.2%)	938 (66.5%)	**< 0.001**
Extrathyroidal extension	49 (12.4%)	494 (35.0%)	**< 0.001**
Contrast-enhanced ultrasound	71 (18.0%)	194 (13.7%)	**0.034**
Lymph node location			
Level II	17 (4.3%)	125 (8.9%)	**< 0.001**
Level III	98 (24.9%)	539 (38.2%)	
Level IV	274 (69.5%)	712 (50.5%)	
Level V	5 (1.3%)	35 (2.5%)	

Abbreviations: PTC, papillary thyroid carcinoma; TSH, thyrotropin

[a] Chi-square test; [b] Mann-Whitney U test; [c] Student's t test

Statistical analysis

Categorical variables were presented as frequency and percentages (%) of cases, and the chi-square test or Fisher's exact test was used to compare differences. Continuous variables were presented as either the mean and standard deviation or the median and interquartile range (IQR) of cases. Statistical analyses were conducted using either Student's t-test or the Mann–Whitney U test, as appropriate. All statistical analyses were using SPSS 26.0 for Windows (IBM SPSS, Inc. Chicago, IL, USA) and GraphPad Prism 9.5.0 for Windows (GraphPad software, San Diego, CA, USA). Univariable and multivariable logistic regression analyses determined the independent risk US features for cervical metastatic LNs. The threshold for statistically significance was $p < 0.05$.

The risk stratification model for cervical metastatic LNs was developed using R version 3.6.3 and assessed through receiver operating characteristic (ROC) curve analysis with 5-fold cross-validation to determine discrimination ability. Additionally, calibration plots were used to evaluate predicted probabilities, while decision curve analysis (DCA) and clinical impact curve (CIC) were employed to assess the model's utility in applications.

Results

Clinicopathological characteristics of the candidates

A total of 1665 PTC patients were enrolled, including 373 PTC patients without detected malignant LNs and 1292 PTC patients with detected malignant LNs. Among the 373 PTC patients without malignant LNs, there were 102 males (27.3%) and 271 females (72.7%), with a median (IQR) age of these patients is 43 (range, 33–52), and 318 patients (85.3%) were under 55 years. In contrast, it is 37 (range, 30–47) in 1292 PTC patients with malignant LNs, including 440 males (34.1%) and 852 females (65.9%), and 1155 patients (89.4%) are younger than 55 years (Table 1).

All the 1806 LNs from the 1665 PTC patients were detected, and the results exhibited that 394 cases were benign LNs and 1411 cases were malignant LNs. In the 394 cases with benign LNs, the median (IQR) tumor size is 11 (mm) (range, 8–16), with195 cases (49.5%) ≤ 10 (mm), whereas in the 1,411 malignant LNs, the median size was 17 mm (range, 11–25), and 292 cases (20.7%) were ≤ 10 (mm) ($p < 0.001$). Moreover, the ratio of multifocality ($p = 0.006$), bilateral tumor ($p < 0.001$), capsular invasion ($p < 0.001$), and extrathyroidal extension ($p < 0.001$) was significantly higher in malignant LN cases compared to benign LN cases, while the proportion of contrast-enhanced ultrasound was lower than that of benign LNs cases ($p = 0.034$). Additionally, the detected location of malignant LNs were extremely different from those of benign LNs, in which benign LNs were less frequently detected in levels II and IV than malignant LNs, and more frequently detected in levels IV ($p < 0.001$).

Comparison of the US features of benign and malignant lymph nodes in PTC

Table 2 summarizes a comparison of US features among benign and malignant LNs in PTC patients. In unadjusted univariate logistic regression analysis, all features, except for indistinct marginal, showed an important link with malignancy. However, in adjusted multivariable logistic regression analysis, the absence of fatty hilum (odds ratio [OR], 9.62; 95% CI, 5.82–15.89; $p < 0.001$), cystic components (OR, 4.96; 95% CI, 2.64–9.32; $p < 0.001$), round shape (SD/LD ≥ 0.5) (OR, 1.66; 95% CI, 1.25–2.19.1, $p < 0.001$), abnormal vascularity (OR, 7.03; 95% CI, 4.44–11.13; $p < 0.001$), hyper and hypo-echogenicity (OR, 4.48; 95% CI, 1.47–13.66; $p = 0.008$), hyper-echogenicity (OR, 19.61; 95% CI, 2.17–177.40; $p = 0.008$), microcalcification (OR, 8.02; 95% CI, 5.16–12.46; $p < 0.001$), and macrocalcification (OR, 2.56; 95% CI, 1.53–4.30; $p < 0.001$) were malignancy features, showing risks of malignant LNs. These suspicious US features are shown in Fig. 1. LNs with these suspicious US features have a higher malignancy risk.

Diagnostic efficacy of suspicious US feature for cervical metastatic lymph node in PTC patients

We evaluated the diagnostic efficacy of these suspicious US features for cervical metastatic LNs in PTC, and found that the majority of features had high specificity (Table 3). The absence of fatty hilum had the highest sensitivity (98.16%) and accuracy (83.32%) among these features, but with the lowest specificity (30.20%). For specificity, all US features, except absence of fatty hilum and round shape, were high. In our study, all suspicious US features had high positive predictive values (PPV), of which the lowest (83.32%) was beyond 83.00%. These features had low negative predictive values (NPV), except absence of fatty hilum (82.07%). The false negative rates (FPR) of these features were under 20.00%, of which the highest was 16.68%. The FNRs of all features, except the absence of fatty hilum, were beyond 60.00%. Most of these features had a great accuracy and five of them were beyond 50.00%.

Diagnostic efficacy of non-suspicious US feature for cervical metastatic lymph node in PTC patients

We developed a predictive model based on suspicious US radiologic features for cervical metastatic lymph nodes in PTC patients (Seen in Fig. 2). The predictive model combined different and sophisticated situations to predict the metastatic risk of cervical LN by calculating the total score of suspicious US features in PTC patients. In a word, the greater number of suspicious US features, if PTC patients have, the higher metastatic risk of cervical LN.

To evaluate the performance of the predictive model, we use multiple evaluation methods for validation in Fig. 3. Seen from Fig. 3A, Mean ROC (area = 0.84) indicated that this model correctly distinguishes patients with corresponding clinical outcomes from patients without clinical outcomes. We used calibration curve to evaluate the accuracy of this nomogram in predicting the probability of developing clinical outcomes in individuals. The

Table 2 Comparison of US features among benign and malignant lymph nodes in PTC patients

US features	Unadjusted		Multivariable adjusted	
	Prevalence OR (95% CI)	*P* value	Prevalence OR (95% CI)	*P* value
Absence of fatty hilum	23.05 (14.79–35.92)	**< 0.001**	9.62 (5.82–15.89)	**< 0.001**
Cystic components	9.67 (4.81–15.62)	**< 0.001**	4.96 (2.64–9.32)	**< 0.001**
Irregular shape	1.84 (1.28–2.63)	**< 0.001**	1.03 (0.64–1.65)	0.908
Indistinct marginal	1.35 (0.81–2.24)	0.253	1.32 (0.67–2.57)	0.422
Round shape (SD/LD ≥ 0.5)	1.88 (1.50–2.36)	**< 0.001**	1.66 (1.25–2.19)	**< 0.001**
Echo-heterogeneity	2.04 (1.62–2.57)	**< 0.001**	1.03 (0.77–1.38)	0.841
Abnormal vascularity	11.41 (7.45–17.47)	**< 0.001**	7.03 (4.44–11.13)	**< 0.001**
Echogenicity				
Hypo-echogenicity	1 [Reference]	**< 0.001**	1 [Reference]	**< 0.001**
Iso-echogenicity	9.83 (1.34–72.22)	**0.025**	6.15 (0.79–47.86)	0.083
Hyper- and hypo-echogenicity	8.88 (3.25–24.22)	**< 0.001**	4.48 (1.47–13.66)	**0.008**
Hyper-echogenicity	13.95 (1.92–101.57)	**0.009**	19.61 (2.17–177.40)	**0.008**
Calcifications				
Absent	1 [Reference]	**< 0.001**	1 [Reference]	**< 0.001**
Microcalcifications	12.56 (8.31–19.00)	**< 0.001**	8.02 (5.16–12.46)	**< 0.001**
Macrocalcification	4.87 (3.01–7.87)	**< 0.001**	2.56 (1.53–4.30)	**< 0.001**

Abbreviations: LD, long diameter; OR, odds ratio; PTC, papillary thyroid carcinoma; SD, short diameter; US, ultrasound

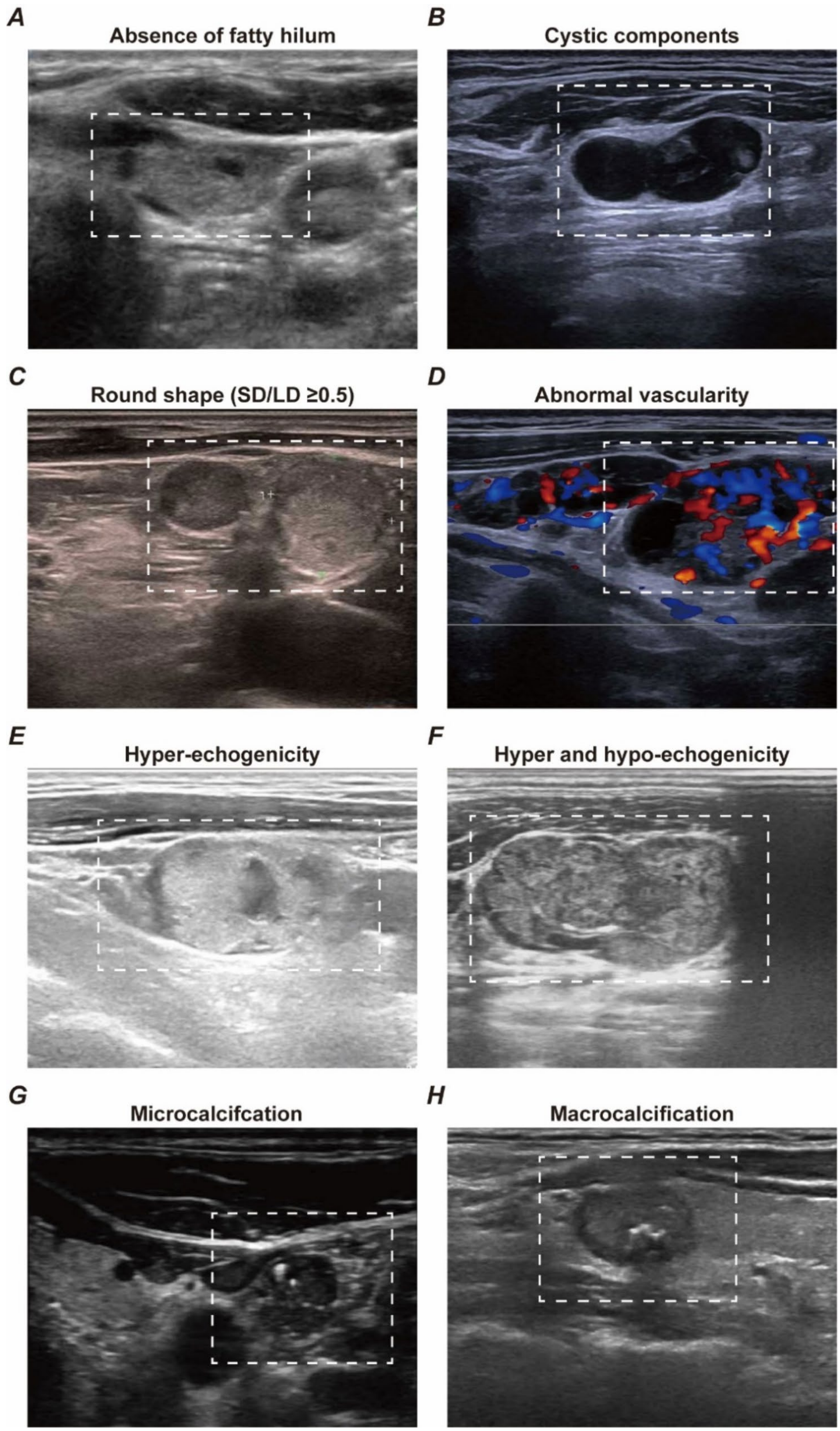

Fig. 1 Eight US features of PTC patients. **(A)** absence of fatty hilum; **(B)** cystic components; **(C)** round shape (SD/LD ≥ 0.5); **(D)** abnormal vascularity; **(E)** hyper-echogenicity; **(F)** hyper and hypo-echogenicity; **(G)** microcalcification; **(H)** macrocalcification

Table 3 The diagnostic efficacy of suspicious US feature for cervical metastatic lymph node in PTC patients

Suspicious US feature	Sensitivity	Specificity	PPV	NPV	FPR	FNR	Accuracy
Absence of fatty hilum	98.16%	30.20%	83.43%	82.07%	16.57%	17.93%	83.32%
Cystic components	21.40%	96.95%	96.18%	25.62%	3.82%	74.38%	37.89%
Round shape (SD/LD ≥ 0.5)	55.21%	60.41%	83.32%	27.36%	16.68%	72.64%	56.34%
Abundant vascularity	42.52%	93.91%	96.15%	31.33%	3.85%	68.67%	53.74%
Hyperechogenicity	11.06%	98.73%	96.89%	23.66%	3.11%	76.34%	30.19%
Hyper- and hypo-echogenicity (non-uniformity)	8.19%	98.98%	96.55%	23.66%	3.45%	76.34%	28.47%
Hyper-echogenicity (uniformity)	3.39%	99.74%	97.78%	23.66%	2.22%	76.34%	25.64%
Calcifications	54.93%	88.32%	94.40%	35.37%	5.60%	64.63%	62.22%
Microcalcification	48.42%	93.05%	95.83%	35.37%	4.17%	64.63%	58.81%
Macrocalcification	21.87%	94.57%	89.90%	35.37%	10.10%	64.63%	44.50%

Abbreviations: FPR, false positive rate; FNR, false negative rate; PPV, positive predictive value; NPV, negative predictive value; LD, long diameter; PTC, papillary thyroid carcinoma; SD, short diameter; US, ultrasonography

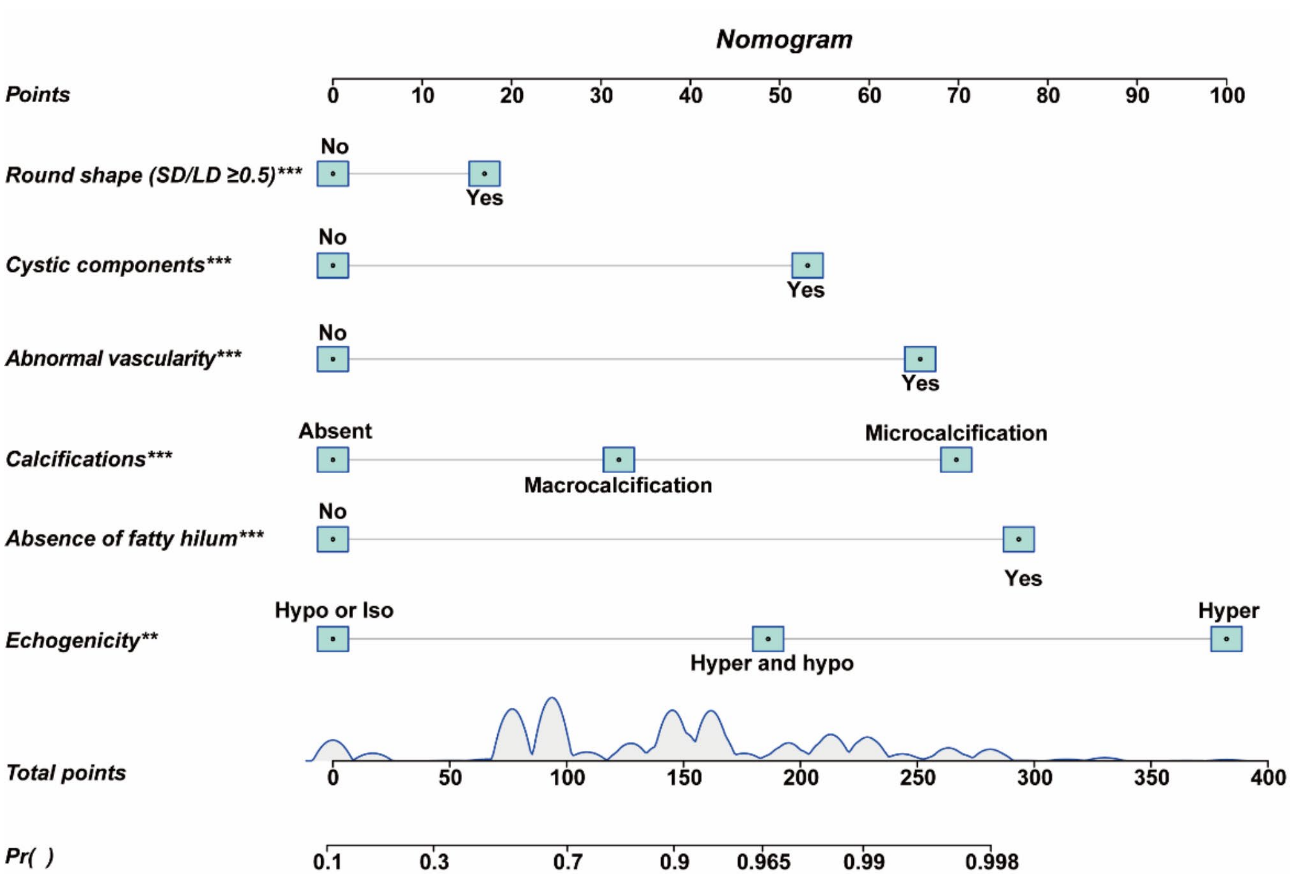

Fig. 2 A nomogram for all features with multiple conditions

actual curve was basically close to the ideal curve, which indicated that the predicted risk of clinical events by this model were in good agreement with the actual condition in our cohorts (Fig. 3B). We performed the decision curve analysis (DCA) and clinical impact curve to assess the improvement the model brings to decision-making in Fig. 3C and D, showing that this model has a great application value.

Improvement and verification of the risk stratification system based on US radiologic features for cervical metastatic lymph nodes in PTC patients

Based on the predictive model, we established a simpler risk stratification system for cervical metastatic LNs in PTC patients in Table 4. In our cohorts, except for 93 cases with non-suspicious US features, we found only two of them had malignancy LNs. The actual malignancy rate was 2.2%, and the system predicted malignancy risk was 10.7%. For other cases with suspicious US features,

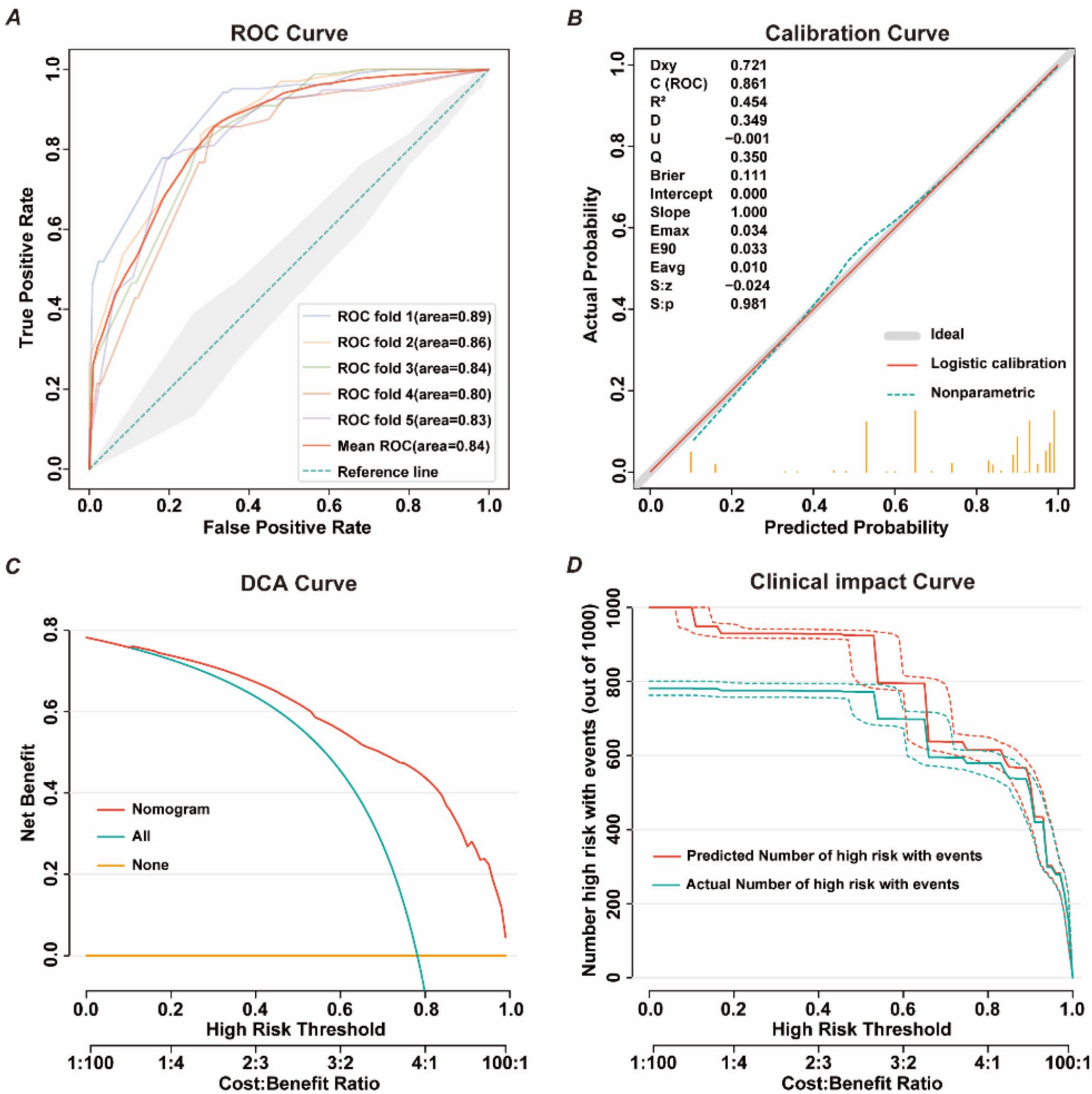

Fig. 3 Validation of the nomogram. **(A)** 5-fold ROC Curve; **(B)** Calibration Curve; **(C)** Decision Clinical Analysis (DCA) Curve; **(D)** Clinical impact Curve

the risk stratification system predicted malignancy risk of having any one, two, three, four, five, or six of suspicious US features was 23.4 – 75.1%, 33.8 – 95.7%, 68.3 – 99.4%, 91.2 – 99.9%, 98.6 – 100.0%, and 99.9 – 100.0%, respectively, which in line with the actual conditions.

In addition, we made the comparison of predictive efficiency for cervical metastatic LNs between risk stratification system and K-TIRADS and ETA Category system in Table 5. According to the K-TIRADS Category system, there were three categories: normal, indeterminate, and suspicious. The actual malignancy rate of them was 8.7%, 61.4%, and 93.2%, respectively, while the system predicted malignancy risk was 10.7 – 16.5%, 53.7 – 65.7%, and 33.6 – 100.0%. For the category of ETA criteria, the actual malignancy rates of categories, including probably benign, indeterminate, suspicious, and not specified, were 2.2%, 64.9%, 94.4%, and 29.8%, respectively, while the system predict malignancy risk was 10.7 – 23.6%, 65.7 – 83.2%, 36.6 – 100.0%, 48.8%.

Table 4 The predictive efficiency of the risk stratification system for cervical metastatic lymph node in PTC patients

Suspicious US features	No. of Cases	No. of Malignancy LNs	Actual Malignancy rate (%)	Predicted Malignancy risk (%)
None of suspicious US features	93	2	2.2%	0-10.7%
Any one of the following suspicious US features	278	149	53.6%	23.4 – 75.1%
Absence of fatty hilum	232	132	56.9%	53.7%
Cystic components	1	1	100.0%	36.6%
Round shape (SD/LD ≥ 0.5)	34	9	26.5%	16.5%
Hyperechogenicity				
Hyper and hypo-echogenicity (non-uniformity)	1	1	100.0%	33.6%
Hyper-echogenicity (uniformity)	2	2	100.0%	69.8%
Calcifications				
Microcalcification	2	1	50.0%	48.5%
Macrocalcifications	–	–	–	23.6%
Abundant vascularity	6	4	66.7%	45.6%
Any two suspicious US features	569	433	76.1%	33.8 – 95.7%
Any three suspicious US features	487	452	92.8%	68.3 – 99.4%
Any four suspicious US features	267	264	98.9%	91.2 – 99.9%
Any five suspicious US features	96	96	100.0%	98.6 – 100.0%
All of six suspicious US features	15	15	100.0%	99.9 – 100.0%

Abbreviations: PTC, papillary thyroid carcinoma; LD, long diameter; SD, short diameter; US, ultrasonography

Table 5 Comparison of predictive efficiency for cervical metastatic lymph node between the risk stratification system and K-TIRADS and ETA Category system

Category system	No. of Cases	No. of Malignancy LNs	Actual Malignancy rate (%)	Nomogram predicted Malignancy risk (%)
Total	1805	1411	79.8%	
K-TIRADS				
Normal	127	11	8.7%	10.7 – 16.5%
Indeterminate	515	316	61.4%	53.7 – 65.7%
Suspicious	1163	1084	93.2%	33.6 – 100.0%
ETA				
Probably benign	93	2	2.2%	10.7 – 23.6%
Indeterminate	393	318	64.9%	65.7 – 83.2%
Suspicious	1081	1020	94.4%	36.6 – 100.0%
Not specified	238	71	29.8%	48.8%

Abbreviations: ETA, European Thyroid Association; K-TIRADS, Korean Thyroid Imaging Reporting and Data System; LN, Lymph Node

Discussion

This study identified eight suspicious ultrasound (US) features associated with cervical metastatic lymph nodes (LNs) in patients with papillary thyroid carcinoma (PTC). These features include the absence of fatty hilum, cystic components, round shape (SD/LD ≥ 0.5), abnormal vascularity, hyper-echogenicity, a combination of hyper- and hypo-echogenicity, microcalcification, and macrocalcification. Contrarily, irregular shape and indistinct margins did not significantly predict metastasis, despite being considered suspicious for metastatic LNs in previous studies [20–22]. Additionally, we developed a risk stratification system based on these suspicious US features to predict cervical metastatic LNs in PTC patients, offering a more efficient and straightforward method for clinicians to assess LN status.

With the increasing detection rates of thyroid cancer, the age of affected patients is becoming younger. This trend has also led to more personalized approaches for diagnosing and treating thyroid cancer [23, 24]. While PTC generally has a favorable prognosis, it tends to metastasize to LNs early [25, 26], highlighting the importance of a risk stratification system that aids in timely intervention. We identified eight independent imaging features associated with metastatic LNs in thyroid cancer, which can be used to assess the risk of metastatic LNs based on these suspicious imaging features. In our results, these eight features demonstrated high positive predictive values for metastatic LNs (83.32-97.78%), with most also showing high predictive accuracy. Notably, the absence of a fatty hilum showed the highest sensitivity (98.16%) and accuracy (83.32%), though it had the lowest specificity (30.20%). Conversely, the hyper-echogenicity feature exhibited the highest specificity (99.74%), but the lowest sensitivity (3.39%) and accuracy (25.64%).

Previous studies have indicated five US features-the absence of a hilum, cortical hyperechogenicity, cystic changes, abnormal vascular patterns, and punctate echogenic foci-as independent ultrasound features suggestive of metastatic LNs in thyroid cancer [27, 28]. In this study, we incorporated a larger sample size and analyzed more specific US imaging features. Our results revealed three additional suspicious US features associated with metastatic LNs that had not been reported in prior studies: a round shape (SD/LD ≥ 0.5), a combination of hyper- and hypo-echogenicity, and macrocalcification. While these features did not stand out in terms of their overall diagnostic performance for metastatic LNs, they were identified as independent predictors in multivariate analysis. It is important to note that irregular shape has been regarded as a suspicious feature for metastatic LNs in several guidelines [29, 30]. However, our findings suggest that irregular shape is not an independent suspicious feature for predicting metastatic LNs. Furthermore, in both unadjusted and multivariate regression analyses, indistinct margins were also not found to be an independent feature of malignant LNs.

To assess the comprehensive diagnostic effectiveness of these ultrasound features for metastatic LN, we categorized suspicious US features based on the number of suspicious characteristics present: none (0-10.7%), any one (23.4-75.1%), any two (33.8-95.7%), any three (68.3-99.4%), any four (91.2-99.9%), any five (98.6-100.0%), and all of six (99.9-100.0%). When four or more suspicious US features were present, the predicted risk of metastatic LNs was high. To more objectively and specifically estimate the predictivity efficiency of these suspicious US features for metastatic LNs in PTC, we developed a risk stratification system. The results of a five-fold ROC analysis showed a strong alignment between the predicted and actual results. Additionally, the calibration curve demonstrated that the actual curve closely matched the ideal curve, confirming the system's good calibration. Decision curve analysis (DCA) indicated that the risk stratification system has significant practical application. Our verification showed that the predictions of the system were consistent with actual outcomes. Given the high incidence of LN metastasis and its negative impact on prognosis, clinicians should closely examine the suspicious ultrasound features of LNs and consider performing fine needle aspiration (FNA) biopsies more proactively.

Additionally, we made a comparison of predictive efficiency for cervical metastatic LNs between our model and K-TIRADS and ETA Category system. As far as we know, both the ETA guide and K-TIRADS Category system provides effective risk stratification, with strong correlation between them [17, 18]. While both categorize LNs into three risk categories, each category corresponds to different suspicious ultrasound features. Moreover, both systems classify LNs with the absence of fatty hilum as an indeterminate. Moreover, 29.8% of metastatic LNs in our study be classified to not specified by the ETA system. These factors make it complicated in practical application. Our study proposes a more personalized LNs risk classification system that allows clinicians to dynamically calculate the cumulative risk of multiple suspicious ultrasound features. Compared to existing classification systems, our stratification system may help reduce the missed diagnosis of small and suspicious LN.

One of the limitations of this study is its retrospective design, which may introduce an unavoidable selection bias in the selection of lymph nodes (LNs) for ultrasound-guided biopsy. Furthermore, the use of different ultrasound machines and operators could influence classification and biopsy outcomes, potentially leading to operator-related observational bias. Additionally, the accuracy of ultrasound assessments based on static images from electronic medical records presents inherent limitations. Lastly, fine needle aspiration (FNA) was conducted in only a limited number of cases, which could lead to an overestimation of the malignancy risk for entire cohort, including both benign and uncertain LN groups. The ultrasound technique may also fail to detect smaller lymph nodes.

Conclusions

In summary, our study introduces a novel risk stratification model based on ultrasound radiologic features to predict cervical metastatic lymph nodes in PTC patients. This model could assist surgeons in effectively assessing the status of cervical lymph nodes.

Abbreviations

ATA	American Thyroid Association
CLNM	Central lymph node metastasis
cN+	Clinically lymph nodes positive
cN-	Clinically lymph nodes negative
cNx	Clinically lymph nodes undetected
CT	Computed tomography
ETA	Korea Thyroid Association
ETE	Extrathyroidal extension
FPR	False positive rate
FNR	False negative rate
HT	Hashimoto's thyroiditis
LLNM	Lateral lymph node metastasis
LND	Lymph nodes dissection
NPV	Negative predictive value
PPV	Positive predictive value
PTC	Papillary thyroid carcinoma
TC	Thyroid carcinoma
TT	Total thyroidectomy
US	Ultrasonography

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Author contributions

H.L.T. and S.L.D. conceived and designed the study; H.L.T. and Q.H. carried out experiments; S.L.D. and Z.J.Z. analyzed the data; H.L.T., S.L.D., P.H., and S.C. made the figures; H.L.T. and S.L.D. drafted and revised the paper; H.L.T., P.H. and S.C. reviewed the paper; all authors approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Review Committee of Xiangya Hospital, Central South University, and followed the Declaration of Helsinki (20211245). The informed consent was waived because of the retrospective and anonymous nature of the study.

Consent for publication
All authors gave consent for the publication of this study.

Generative AI and AI-assisted technologies in the writing process
During the preparation of this work the authors used no tools. The authors reviewed and edited the content as needed by themselves and take full responsibility for the content of the publication.

Competing interests
The authors declare no competing interests.

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