Original Article

Risk factors and nomogram to predict skip metastasis in papillary thyroid carcinoma

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Background: Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy. Skip metastases of PTCs are easily misdiagnosed before surgery, and it could lead to re-operation and affect the prognosis. Although there are a few studies about nomograms for predicting central lymph node metastases (CLNM) or lateral lymph node metastases (LLNM) of PTCs, there are few studies about nomograms for skip metastases. Based on the clinical and ultrasonographic characteristics of patients with PTCs, the aim of our study was to investigate the risk factors and establish a nomogram for predicting the risk of skip metastases in PTCs.

Methods: This study enrolled 218 PTCs patients with lateral cervical lymph node metastases and their data were analyzed retrospectively. According to the postoperative pathological results, the patients were divided into skip-positive group and skip-negative group. In order to establish the nomogram, univariate and multivariate analyses were used to estimate risk factors of skip metastases. The receiver operating characteristic (ROC) curve, internal calibration plot and decision curve analysis (DCA) were used to evaluate the nomogram model's efficacy.

Results: There were statistical differences between skip-positive group and skip-negative group in tumor location, the maximum diameter (D) and capsule invasion ($P<0.05$). No statistical differences were observed in sex, age, Hashimoto's thyroiditis, multifocality, anteroposterior diameter/transverse diameter (A/T) ratio, shape, margin, microcalcification, intra-nodular vascularity and preoperative serum thyroglobulin (Tg) ($P\geq0.05$). The risk factors of skip metastases in PTCs were D ≤10 mm, location in the upper portion and capsule invasion. The area under the curve (AUC) of nomogram was 0.877, the accuracy was 85.32%, the sensitivity was 60.98%, and the specificity was 90.96%. The calibration curve and the Hosmer-Lemeshow goodness of fit test showed that the consistency between the nomogram and the actual observation was good. The DCA showed that most PTC patients might benefit from the predictive nomogram model.

Conclusions: A nomogram for predicting skip metastases in PTCs may be useful in clinical diagnosis and treatment.

Keywords: Ultrasound; papillary thyroid carcinoma (PTC); lymph node; skip metastasis; nomogram

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Introduction

The incidence of thyroid carcinoma has been increasing in these years. Papillary thyroid carcinoma (PTC) is the most common pathological type while the rate of cervical lymph node metastasis is 12–81% (1,2). The metastatic pathway of PTC is generally continuous: it firstly invades the central lymph node (CLN), then the ipsilateral lateral lymph node (LLN), and finally involves the contralateral LLN and mediastinal lymph node (3,4). Skip metastases are defined as metastases in the LLN without CLN and the incidence of skip metastases is 6.5–27.5% (5). The 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer recommended therapeutic lateral lymph node dissection (LLND) only for patients with biopsy-proven lateral cervical lymph node metastases (6). When intraoperative pathology indicates negative of CLN, further LLND will not be performed unless preoperative ultrasound and fine needle aspiration biopsy (FNAB) indicate lateral lymph node metastases (LLNM). However, preoperative assessment of LLNM has a certain false negative rate, and its accuracy largely depends on the experience of pathologists and ultrasound doctors (7). Misdiagnosis of skip metastasis of PTCs before surgery will mean insufficient lymph node dissection during surgery, which could lead to re-operation and affect the prognosis. Therefore, the preoperative prediction of skip metastasis is very important for clinical management.

The nomogram models using regression analysis are frequently used in the study of tumor prognosis (8,9). These models which are based on multivariable analysis and integrate the results of logistic or Cox regression could predict the probability of clinical events by providing graphical presentations (8). Compared with traditional evaluation methods, nomogram model could produce more accurate and intuitive predictions. Although there are a few studies about nomograms for predicting CLN metastases (CLNM) or LLNM of PTCs (10,11), there are few studies about nomograms for skip metastases. The aim of our study is to establish a nomogram model according to the clinical and ultrasonographic characteristics of skip metastases in PTCs and evaluate its predictive value. We present this article in accordance with the TRIPOD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-376/rc).

Highlight box

Key findings

- This study found that the risk factors of skip metastasis in papillary thyroid carcinoma (PTC) were the maximum diameter (D) ≤10 mm, location in the upper portion and capsule invasion. The area under the curve of nomogram was 0.877, the accuracy was 85.32%, the sensitivity was 60.98%, and the specificity was 90.96%.

What is known and what is new?

- Skip metastasis in PTC is easily misdiagnosed before surgery, and it could lead to re-operation and affect the prognosis. The preoperative prediction of skip metastasis is very important for clinical management.
- Although there are a few studies about nomograms for predicting central lymph node metastases or lateral lymph node metastases of PTCs, there are few studies about nomograms for skip metastases. In this study, a nomogram was established to predict the risk of skip metastasis in PTC according to the clinical and ultrasonographic characteristics.

What is the implication, and what should change now?

- When PTC is located at the upper portion of thyroid, D ≤10 mm with capsule invasion, clinicians should be vigilant about the possibility of skip metastasis of cervical lymph nodes. The nomogram may be helpful to provide reference to clinical treatment decision-making.

Methods

Patients

This retrospective study was approved by the Ethics Committee of Ruijin Hospital Luwan Branch, Shanghai Jiao Tong University School of Medicine (Approval code: 2022-006), individual consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The clinical and ultrasonographic characteristics of 311 patients with PTCs in Ruijin Hospital Luwan Branch from January 2017 to December 2021 were retrospectively analyzed.

Patients who met all of the following inclusion criteria were enrolled: (I) patients who underwent ultrasonography within 2 weeks before the first thyroid surgery; (II) PTC with LLNM was confirmed by postoperative pathology; (III) patients who did not receive radiotherapy and chemotherapy before ultrasound examination; (IV) thyroid function was tested in the patients. The exclusion criteria were as follows: (I) PTC with CLNM only; (II) patients who had the history of thyroid surgery; (III) the quality of image was poor or the clinical data were incomplete; (IV) patient with distant metastasis or other primary malignant

Table 1 Baseline data of the cohort

Variable	Value
Mean age, years	42.38
Gender	
Male	82 (37.6)
Female	136 (62.4)
Skip-positive group	41 (18.8)
Single region (n=8)	
III	5
IV	3
Two regions (n=14)	
II + III	5
III + IV	9
Three regions (n=18)	
II + III + IV	16
III + IV + V	1
II + IV + V	1
Four regions (n=1)	
II + III + IV + V	1
Skip-negative group	177 (81.2)

Values are presented as n or n (%).

tumor. After screening, a total of 218 eligible patients were enrolled.

Instruments and methods

All ultrasound examinations were performed by a real-time ultrasound instrument (Aplio500, Toshiba), equipped with a 5–14 MHz transducer. The patients were asked to lie on the back with the neck fully exposed. The ultrasonographic characteristics were carefully evaluated, including Hashimoto's thyroiditis (yes or no), multifocality (yes or no), tumor location (upper, middle, lower or isthmus), the maximum diameter (D) of tumor (D ≤10 or >10 mm), shape (irregular or regular), margin (ill-defined or well-defined), anteroposterior diameter/transverse diameter (A/T) ratio (A/T <1 or A/T ≥1), microcalcification (yes or no), intra-nodular vascularity (yes or no) and capsule invasion which meant that the shortest distance from the tumor boundary to the thyroid capsule or trachea was 0 mm (yes or no) (12).

The ultrasound images of each patient were retrospectively reviewed by two experienced radiologists with more than ten years of experience in thyroid ultrasound imaging who were blinded to the patients' clinical histories and pathological diagnoses. If there were different opinions, the radiologists would consult the superior radiologist and reach an agreement.

Surgical techniques

All patients were operated for the first time. CLN + LLN dissection were performed according to the pathological results of FNAB. If LNM was confirmed by FNAB, the range of dissection was from the upper boundary to the sublingual nerve, from the lower boundary to the subclavian vein and from the lateral boundary to the anterior edge of the trapezius muscle.

According to the post-operative pathological results, the patients were divided into skip-positive group and skip-negative group for further analysis.

Statistical analysis

Statistical analyses were conducted by SPSS for Windows version 25.0 (SPSS Inc., Chicago, IL, USA). Chi-squared test or Fisher exact test was used for categorical variables, and binary logistic regression analysis was used for multivariate analysis. When $P<0.05$, the difference was statistically significant. The nomogram was established by using R Studio software (version 4.1.0). The ROC curve was used to evaluate its effectiveness. The calibration curve and the Hosmer-Lemeshow goodness of fit test ($P>0.05$) were used to analyze the consistency between the nomogram and the actual observation. The decision curve analysis (DCA) quantifying the standardized net benefit at different threshold probabilities was used to evaluate the clinical utility of the nomogram.

Results

Pathological results

There were 82 males and 136 females, with an average age of 42.38±13.04 years (range, 17–78 years). There were 41 cases in the skip-positive group, including 8 cases involving single region, 14 cases involving two regions, 18 cases involving three regions, and 1 case involving four regions, and there were 177 cases in the skip-negative group. The characteristics of our cohort are summarized in *Table 1*.

Univariate analysis of clinical and ultrasonographic characteristics between skip-positive group and skip-negative group

The univariate analysis results of clinical and ultrasonographic characteristics are listed in *Table 2*. There were statistical differences in tumor location, D and capsule invasion between skip-positive group and skip-negative group (P<0.05). No statistical differences were observed in sex, age, Hashimoto's thyroiditis, multifocality, A/T ratio, shape, margin, microcalcification, intra-nodular vascularity and preoperative serum thyroglobulin (Tg) (P>0.05) (*Table 2*).

Multivariate analysis between skip-positive group and skip-negative group

The multivariate analysis results are listed in *Table 3*. The upper portion [odd ratio (OR) =3.113, 95% confidence interval (CI): 0.672–14.417], D ≤10 mm (OR =3.84, 95% CI: 1.572–9.378) and capsule invasion (OR =8.07, 95% CI: 2.983–21.835) were independent risk factors for skip metastases (P<0.05) (*Figure 1*).

Nomogram for predicting skip metastases of cervical lymph nodes in PTCs

The nomogram was established according to the results of multivariate logistic regression analysis (*Figure 2*). Each risk factor could be scored. When PTC was located in the upper portion, it was 100 points, 9 points in the middle portion, 0 points in the lower portion and 58 points in the isthmus; 49 points when D ≤10 mm and 0 point when D >10 mm; 77 points for capsule invasion and 0 point for PTC without capsule invasion. The total points (line 5) could be obtained by summing the points of risk factors. The total points of each patient could generate the risk probability of skip metastasis on the corresponding risk axis (line 6) (*Tables 4,5*).

The area under curve (AUC) of the model was 0.877, and the accuracy, sensitivity and specificity were 85.32%, 60.98%, and 90.96%, respectively (*Figure 3*). The internal calibration plot showed that the predicted results of nomogram were basically consistent with the actual results (*Figure 4*). The Hosmer-Lemeshow goodness of fit test also showed the good consistency between the predicted and actual results (χ^2=2.267, df=5, P=0.811). The DCA was used to assess the net benefit of nomogram-assisted decisions at different threshold probabilities. In the DCA, the nomogram achieved a greater net benefit than having all patients or none patients with a range of the threshold probability ranged from 0.02 to 0.88 (*Figure 5*). This result showed that the use of nomogram to predict skip metastasis in PTC patients would improve the detection rate of skip metastases and patients might benefit from this model.

Discussion

The 2015 American Thyroid Association (ATA) guidelines

Table 2 Univariate analysis of clinical and ultrasonographic characteristics of patients with skip metastases

Clinical and ultrasonographic characteristics	Skip-positive group	Skip-negative group	P value	χ^2
Sex			0.611	0.259
Male	14	68		
Female	27	109		
Age (years)			0.615	0.974
<45	23	109		
45–55	12	39		
>55	6	29		
Hashimoto's thyroiditis			1.000	0.000
Yes	4	16		
No	37	161		

Table 2 (*continued*)

Table 2 (*continued*)

Clinical and ultrasonographic characteristics	Skip-positive group	Skip-negative group	P value	χ^2
Multifocality			0.407	0.687
Yes	21	78		
No	20	99		
Location			<0.001	41.137
Isthmus	3	8		
Upper	30	39		
Middle	6	95		
Lower	2	35		
A/T ratio			0.215	1.538
<1	31	116		
≥1	10	61		
Shape			0.591	0.289
Irregular	26	120		
Regular	15	57		
Margin			0.677	0.173
Ill-defined	26	106		
Well-defined	15	71		
Microcalcification			0.31	1.031
Yes	31	146		
No	10	31		
D (mm)			<0.001	16.43
≤10	20	33		
>10	21	144		
Capsule invasion			<0.001	21.899
Yes	34	75		
No	7	102		
Intra-nodular vascularity			0.375	0.786
Yes	9	51		
No	32	126		
Tg (ng/mL)			0.135	–
≤77	41	164		
>77	0	13		

A/T, anteroposterior diameter/transverse diameter; D, the maximum diameter; Tg, thyroglobulin.

Table 3 Multivariate logistic regression analysis of clinical and ultrasonographic characteristics of patients between skip-positive group and skip-negative group

Variable	P value	OR	95% CI (lower)	95% CI (upper)
Location	<0.001			
Isthmus as reference				
Upper	0.146	3.113	0.672	14.417
Middle	0.115	0.263	0.05	1.383
Lower	0.127	0.204	0.027	1.571
Capsule invasion	<0.001	8.07	2.983	21.835
D	0.003	3.84	1.572	9.378

OR, odds ratio; CI, confidence interval; D, the maximum diameter.

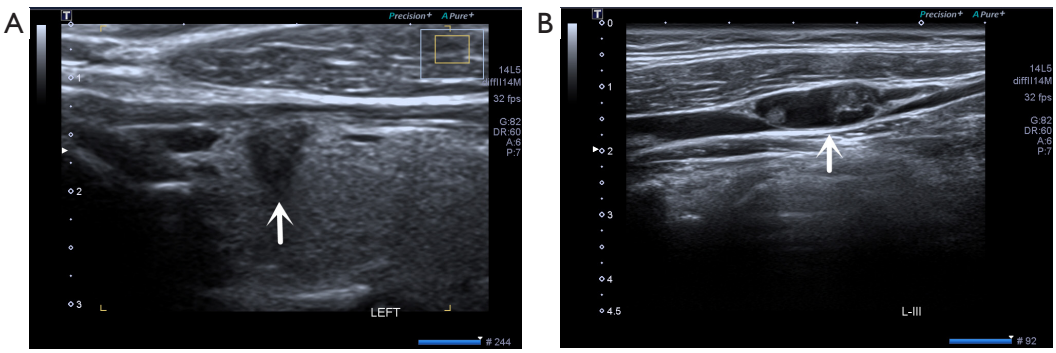

Figure 1 A 39-year-old female patient with skip metastasis of PTC. (A) PTC (the white arrow) located at the upper portion of the thyroid, size 4.9 mm × 5.9 mm, with capsule invasion; (B) lymph node metastasis in level III (the white arrow). PTC, papillary thyroid cancer.

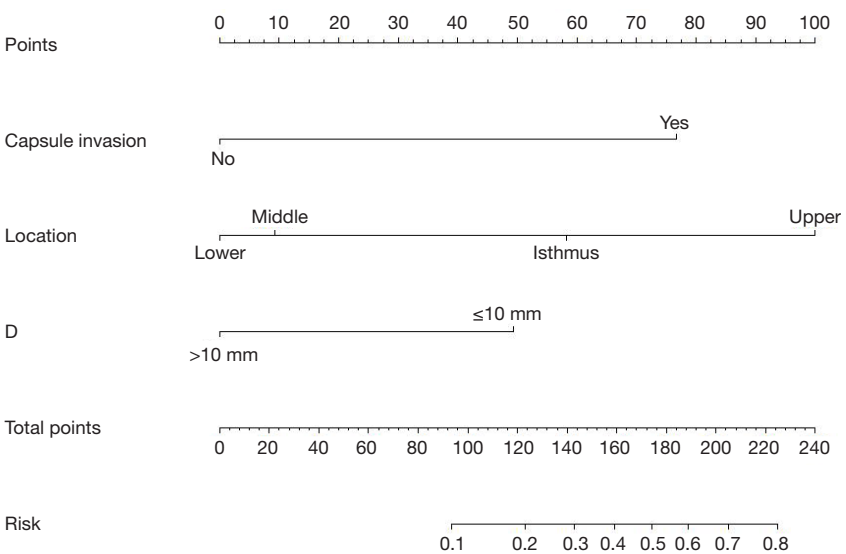

Figure 2 Nomogram for predicting skip metastasis of PTC. D, the maximum diameter; PTC, papillary thyroid cancer.

Table 4 Score of risk factor in nomogram

Risk factor	Classification	Points
Location	Upper	100
	Middle	9
	Lower	0
	Isthmus	58
D (mm)	≤10	49
	>10	0
Capsule invasion	Yes	77
	No	0

D, the maximum diameter.

Table 5 Risk prediction

Total points	Risk
93	0.1
123	0.2
143	0.3
159	0.4
174	0.5
189	0.6
205	0.7
225	0.8

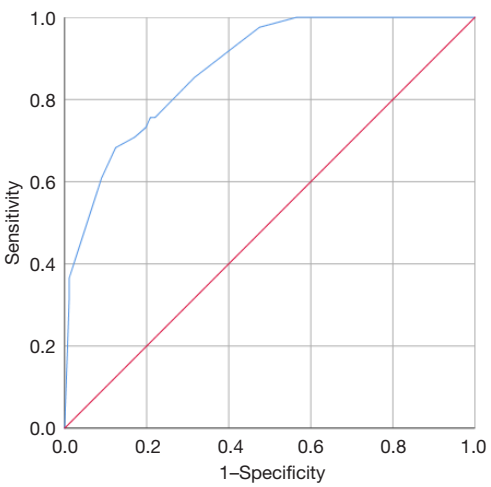

Figure 3 The ROC curve of nomograms for skip metastasis. The AUC was 0.877, the accuracy was 85.32%, the sensitivity was 60.98%, and the specificity was 90.96%. ROC, receiver operating characteristic; AUC, area under the curve.

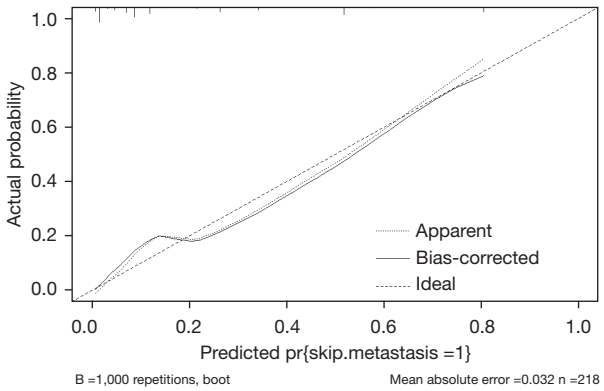

Figure 4 Calibration curves of the nomogram for the probability of skip metastasis. On the calibration, the y-axis represents the actual probability; the x-axis represents the predicted probability of skip metastasis by the nomogram. The three lines in the figure are nomogram, bias-corrected curve and ideal curve respectively.

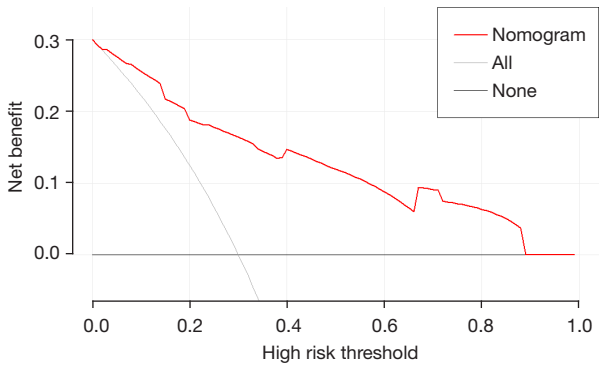

Figure 5 Decision curve analysis for nomogram. The black line represents the hypothesis that all PTC patients have no skip metastasis. The grey line represents the hypothesis that skip metastasis exists in all PTC patients. The red line represents the nomogram. The y-axis represents net benefit, and the x-axis represents threshold probability. PTC, papillary thyroid cancer.

recommended therapeutic LLND only for patients with biopsy-proven LLNM, and the application of prophylactic central-compartment neck dissection (ipsilateral or bilateral) should be careful (6). However, the incidence of skip metastasis in PTC is about 6.5–27.5% (5). Skip metastasis is closely associated to local recurrence and prognosis (13). Re-operation may increase the risk of surgical complications, including recurrent laryngeal nerve injury. Therefore, even if no obvious metastatic lymph nodes are found in the central compartment, the LLN should be carefully evaluated to avoid misdiagnosis of skip metastasis. In order

to screen high-risk patients who may have skip metastasis before surgery, we established a predictive model of skip metastasis. Nomogram can simply and intuitively reflect the relationship between variables in multivariate analysis, and predict the occurrence and prognosis of disease through scoring standards (14-16). This study analyzed the clinical and ultrasonic characteristics of PTCs with skip metastases, and the risk factors were screened out in order to establish the predictive nomogram model.

Univariate and multivariate logistic regression analyses between skip-positive group and skip-negative group showed that PTCs located in the upper portion, D ≤10 mm with capsule invasion were more prone to skip metastases ($P<0.05$). When the tumor is located in the upper portion of thyroid, there might be an independent lymphatic drainage pathway. The lymphatic drainage of the upper pole of the thyroid may follow the upper pole vessels, which directly drains to the lateral region and into the deep vein without passing through the central region (17,18). The study of lymphatic anatomy reported by Likhterov *et al.* (19) also showed the exclusive lymphatic pathway of the upper portion of the thyroid gland. Therefore, the LLN might be the first lymphatic drainage station for upper portion tumor, and it is more prone to skip metastasis. Understanding the pathway of disease spread can provide a better understanding of the reasons for skip metastasis.

Previous studies suggested that skip metastasis was more common in small PTCs such as microcarcinomas, which were consistent with our findings (20,21). Our results showed that D ≤10 mm was a risk factor for skip metastases of PTCs. Zhang *et al.* reported that tumor size was significantly associated with lymph node metastasis (22), and the frequency of CLNM is known to increase with tumor size in PTC (23). Compared with small nodules (D ≤10 mm), large nodules are more invasive, and a wider range of lymph nodes may be involved, which could lead to a higher risk of concurrent CLNM and LLNM (24). Therefore, skip metastasis is less common in large PTC. For the small PTC, it is more likely that only LLN at the first lymphatic drainage station may be involved due to the independent lymphatic drainage pathway.

Capsule invasion is an important risk factor affecting cervical lymph node metastasis. There are abundant blood vessels and lymphatic vessels around the thyroid capsule and between the inner and outer capsule. When the tumor invades the capsule, the barrier effect of the capsule is damaged. The tumor invades the adjacent neck lymph nodes through blood vessels and lymphatic vessels, and even distant metastasis occurs (25). According to the previous studies (17,26), capsule invasion was also considered as a predictive factor of skip metastasis in PTC patients. In addition, the upper pole of thyroid tissue is relatively thin due to the butterfly shape of the thyroid gland. Therefore, even if the tumor is small, it can easily invade the capsule and even extend to the sternothyroid muscle or perithyroid soft tissue if it is located at the upper pole. Our findings showed that PTCs with capsule invasion in the upper pole might have a higher risk of skip metastasis.

Some studies (27,28) showed the important role of serum Tg in predicting node metastasis while the others (7,29) showed that there was weak correlation between Tg and metastatic disease. There is still controversy over whether preoperative serum Tg can predict lymph node metastasis in PTCs. In our study, there was no statistical difference in serum Tg between skip-positive group and skip-negative group.

Nomogram's theory was put forward by French engineer Philbert Maurice d'Ocagne (1862–1938) in 1884 (30). It was first used in engineering. Nomogram is an effective model which transforms the complex regression equation into a visual graph. By integrating different prognosis and determinant variables, nomogram can generate the probability of clinical events and calculate the survival rate of tumor patients (30-32), so it has been widely applied in medical research. Compared with other prediction models, the prediction of nomograms is more accurate and straightforward. Previous studies have used nomogram model to predict CLNM or LLNM in PTCs and achieved good results (10,11). Wang *et al.* reported that the nomogram based on the five variables (age, gender, focal, BRAF and tumor size) could predict the CLNM in PTCs and the ROC curve showed high efficiency (11).

In this study, we selected the risk factors for predicting skip metastases in PTCs patients by multivariate logistic regression analysis. Nomogram could predict skip metastases in PTCs by weighting the points of the risk factors. The larger points in the nomogram indicated higher risk of skip metastasis. We added the points to obtain the total points. Through the function conversion relationship between the total points and the risk of skip metastasis, the predicted value of skip metastasis in PTC patients can be calculated. For example, when PTC was located at the upper portion of thyroid, D ≤10 mm with capsule invasion, the corresponding points of risk factors were 100, 49 and 77, respectively. The total point of nomogram was 226, suggesting that the risk probability of skip metastasis of

PTC cervical lymph nodes would exceed 80%. The AUC of the nomogram established in our study was 0.877. The accuracy, sensitivity and specificity were 85.32%, 60.98%, and 90.96%, respectively. The internal calibration plot and the Hosmer-Lemeshow goodness showed that the predicted results of nomogram were basically consistent with the actual results. Analysis of the decision curve showed that most PTC patients may benefit from the predictive nomogram model.

This study had some limitations. First, because it was a retrospective single center study, there might be deviations in the selection of patients and the input of information. Second, the sample size was small, especially in the skip-positive group. All these need to be further studied by a large sample.

Conclusions

When PTC is located at the upper portion of thyroid, D ≤10 mm with capsule invasion, we should be vigilant about the possibility of skip metastasis of cervical lymph nodes. The nomogram may be helpful to provide reference to clinical treatment decision-making.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-376/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-376/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-376/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This retrospective study was approved by the Ethics Committee of Ruijin Hospital Luwan Branch, Shanghai Jiao Tong University School of Medicine (Approval code: 2022-006), individual consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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