European Journal of Surgical Oncology 45 (2019) 1039–1045

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Individual prediction of lateral neck metastasis risk in patients with unifocal papillary thyroid carcinoma

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ARTICLE INFO

Article history:
Accepted 14 February 2019
Available online 21 February 2019

Keywords:
Nomogram
Lymph node metastasis
Lateral neck
Papillary thyroid carcinoma

ABSTRACT

Introduction: Much controversy exists over whether to perform lateral neck dissection (LND) on patients with papillary thyroid carcinoma (PTC). This study aimed to build predictive nomograms that could individually estimate lateral neck metastasis (LNM) risk and help determine follow up intensity.
Patients and methods: Unifocal PTC patients who underwent LND between April 2012 and August 2014 were identified. Clinical and pathological variables were retrospectively evaluated using univariate and stepwise multivariate logistic regression analysis. Variables that had statistical significance in final multivariate logistic models were chosen to build nomograms, which were further corrected using the bootstrap resampling method.
Results: In all, 505 PTC patients were eligible for analysis. Among these, 178 patients (35.2%) had lateral neck metastasis. Two nomograms were generated: nomogram (c) and nomogram (c + p). Nomogram (c) incorporated four clinical variables: age, tumor size, tumor site, and extrathyroidal extension (ETE). It had a good discriminative ability, with a C-index of 0.79 (bootstrap-corrected, 0.78). Nomogram (c + p) incorporated two clinical variables and two pathological variables: tumor size, tumor site, extranodal extension (ENE), and number of positive nodes in the central compartment. Nomogram (c + p) showed an excellent discriminative ability, with a C-index of 0.86 (bootstrap-corrected, 0.85).
Conclusion: Two predictive nomograms were generated. Nomogram (c) is a clinical model, whereas nomogram (c + p) is a clinicopathological model. Each nomogram incorporates only four variables and can give an accurate estimate of LNM risk in unifocal PTC patients, which may assist clinicians in patient counseling and decision making regarding LND.

Introduction

Patients with papillary thyroid carcinoma (PTC) often harbor cervical lymph node metastasis. One of the most commonly involved regions is the lateral neck [1], which occurs in 25%–65% of PTC patients [2–6].

Therapeutic lateral neck dissection (LND) is recommended for PTC patients with clinically positive lateral neck (cN1b) [7], and prophylactic LND is not routinely recommended for patients with clinically negative (cN0) lateral neck. However, some patients with cN0 lateral neck might need secondary operations due to positive nodes in lateral compartments during surveillance. Such patients may benefit from a risk stratification, which can identify high- and low-risk patient subsets and thus may affect the follow up intensity. However, no such stratification tool has yet been reported.

This paper retrospectively analyzed our data, refined independent predictors, and culminated in predictive nomograms to estimate lateral neck metastasis (LNM) risk individually in unifocal PTC patients.

Patients and methods

Patients

Primary PTC patient-level data registered in the Department of Thyroid and Neck between April 2012 and August 2014 were identified. Among these, patients with unifocal PTC who underwent either hemi- or total thyroidectomy plus neck dissection were

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https://doi.org/10.1016/j.ejso.2019.02.016
0748-7983/

identified. Neck dissection might be prophylactic or therapeutic, and the extent of dissection should include both the central (level VI) and lateral neck (at least ipsilateral levels III and IV) [8,9]. Multifocal PTC patients, as well as those who received only central compartment neck dissection (CCND) or LND, were excluded. This study was approved by our Institutional Review Board.

Clinical and pathological factors were retrospectively collected and analyzed, including gender, age, tumor size, tumor side and site, extrathyroidal extension (ETE), pathological T (pT) classification, preoperative thyroid-stimulating hormone (TSH) level, number of positive nodes in level VI, extranodal extension (ENE) in level VI, and Hashimoto thyroiditis (HT).

Among these, tumor side was classified as right side, left side, or isthmus. Tumor site was grouped as follows: superior third, middle third, inferior third, isthmus, middle and inferior, middle and superior, and whole lobe [3]. Primary tumor size was defined as the largest diameter of primary tumor measured by preoperative ultrasound (US) imaging. ETE was defined as a visible invasion of surrounding soft tissues by intraoperative findings. Pathological T was classified according to the 7th edition of the American Joint Committee on Cancer/International Union for Cancer Control (AJCC/UICC) tumor node metastasis (TNM) staging system (2009). Number of positive nodes, ENE, and HT were diagnosed by routine pathological examination, which was reviewed by two experienced pathologists. The endpoint was lymph node metastasis in the lateral neck.

Statistical analysis

Clinicopathological variables were analyzed using univariate and multivariate logistic regression analysis. Among these variables, age, tumor size, as well as number of positive nodes in level VI, were modeled as continuous variables; the others were modeled as categorical data with a dummy variable. In multivariate models, a backward stepwise variable selection procedure was applied for model selection based on the Akaike information criterion (AIC) [10]. The multivariate model with the lowest AIC was chosen as the best model, and variables in this model were used to build a nomogram. Two nomograms integrating different variables were designed. One nomogram was for preoperative use, while the other one was for postoperative use.

The discriminative ability of each nomogram was quantified by Harrell's concordance index (C-index) [11]. C-index has a similar meaning to the area under a receiver operating characteristic curve (AUC). This highest value of C-index is 1, which means perfect discrimination; the lowest value is 0.5, which stands for random discrimination. Each nomogram was internally validated through a bootstrap procedure, and an optimism-corrected C-index was calculated using 1000 bootstrap resamples to prevent model overfitting [12]. Performance of the nomogram was further assessed by a calibration plot, which plotted the nomogram-predicted probabilities against the observed probabilities. All statistical analysis was performed using R language (http://www.r-project.org/) software and the rms package (https://cran.r-project.org/web/packages/rms/).

Results

Five hundred five unifocal PTC patients undergoing both CCND and LND were identified. The cohort included 366 females and 139 males, with a mean age of 44.07 ± 11.98 years (range, 10–76 years). The demographic and tumor characteristics are presented in Table 1. Overall, 178 patients (35.2%) had metastatic lymph nodes in the lateral neck, 227 (45.0%) had positive nodes in the central neck, and 75 (14.9%) had ENE in one or more lymph node metastases in the central neck. The mean tumor size was 15.28 ± 11.59 mm (range, 3–80 mm). The size of positive nodes in the lateral neck was 9.08 ± 5.66 mm (range 2–29 mm) in the smallest dimension, and the size of negative nodes was 5.62 ± 1.93 mm (range 2–16 mm).

Among 505 PTC patients, 106 (21.0%) had cN + lateral neck, and 399 (79.0%) had cN0 lateral neck by preoperative ultrasonic examination. Among 399 patients with cN0 lateral neck, 93 (23.3%) had positive nodes in the lateral neck, and 306 (76.7%) had negative nodes in the lateral neck, findings established by means of definitive pathology examination.

Table 1
Demographic, clinical and tumor characteristics of 505 PTC patients.

Characteristic	No.	%
Total patients	505	100.0%
LNM		
No	327	64.8%
Yes	178	35.2%
Gender		
Female	366	72.5%
Male	139	27.5%
Age (years)		
Mean ± SD	44.07 ± 11.98	
Range	10 to 76	
<45	253	50.1%
>=45	252	49.9%
Gender and age		
Female and <45	180	35.6%
Female and ≥ 45	186	36.8%
Male and <45	73	14.5%
Male and ≥ 45	66	13.1%
Primary tumor size (mm)		
Mean ± SD	15.28 ± 11.59	
Range	3 to 80	
Side		
Right	285	56.4%
Left	206	40.8%
Isthmus	14	2.8%
Tumor site		
Superior	99	19.6%
Mid	182	36.0%
Inferior	67	13.3%
Isthmus	14	2.8%
Mid and Superior	64	12.7%
Mid and Inferior	60	11.9%
Whole lobe	19	3.8%
Visible ETE		
No	404	80.0%
Yes	101	20.0%
pT classification		
T1a	242	47.9%
T1b	105	20.8%
T2	50	9.9%
T3	61	12.1%
T4	47	9.3%
Preoperative TSH level (mIU/L)		
Mean ± SD	3.85 ± 4.51	
Positive nodes in Level VI		
Mean ± SD	1.17 ± 1.80	
Range	0 to 10	
No	278	55.0%
Yes	227	45.0%
No. of removed nodes in Level VI		
Mean ± SD	4.16 ± 3.25	
Range	0 to 22	
ENE in level VI		
No	430	85.1%
Yes	75	14.9%
HT		
No	393	77.8%
Yes	112	22.2%

Abbreviations: PTC, papillary thyroid carcinoma; LNM, lateral neck metastasis; SD, standard deviation; ETE, extrathyroidal extension; TSH, thyroid-stimulating hormone; pT, pathological T; ENE, extranodal extension; HT, Hashimoto thyroiditis.

In this study, 259 cases were categorized as patients with unifocal micro-PTC, who had a primary tumor of 10 mm or less. Among these, 242 patients (93.4%) were diagnosed with T1a tumors; 76 (29.3%) had positive nodes in level VI, 16 (6.2%) had lymph nodes with ENE in level VI, and 46 (17.8%) had lateral neck metastasis. The mean tumor size in all micro-PTC patients was 7.55 ± 2.11 mm (range 3–10 mm). The demographic and tumor characteristics of 259 micro-PTC patients are shown in Table 2.

In univariate logistic regression analysis, variables associated with a higher risk of LNM included younger age, bigger tumor size, lesions of the superior portion or whole lobe, visible ETE, pT classification, number of positive nodes in level VI, and ENE in level VI. The variables without significant association with LNM included gender, side, preoperative TSH level, and HT (Table 3).

Table 2
Demographic and tumor characteristics of patients with unifocal Micro-PTC.

Characteristic	All patients		With LNM		Without LNM		p value
	No.	%	No.	%	No.	%	
Total No. of Patients	259	100.0%	46	17.8%	213	82.2%	
Gender							0.227[a]
Female	185	71.4%	29	15.7%	156	84.3%	
Male	74	28.6%	17	23.0%	57	77.0%	
Age (years)							
Mean ± SD	45.19 ± 10.18		42.43 ± 10.71		45.79 ± 9.99		0.055[b]
<45	119	45.9%	28	23.5%	91	76.5%	0.038[a]
>=45	140	54.1%	18	12.9%	122	87.1%	
Gender and Age							
Female and <45	79	30.5%	20	25.3%	59	74.7%	0.004[a]
Female and ≥ 45	106	40.9%	9	8.5%	97	91.5%	
Male and <45	40	15.4%	8	20.0%	32	80.0%	0.702[a]
Male and ≥ 45	34	13.1%	9	26.5%	25	73.5%	
Primary tumor size (mm)							
Mean ± SD	7.55 ± 2.11		8.09 ± 2.00		7.43 ± 2.11		0.051[b]
Side							0.500[c]
Right	145	56.0%	29	20.0%	116	80.0%	
Left	105	40.5%	15	14.3%	90	85.7%	
Isthumus	9	3.5%	2	22.2%	7	77.8%	
Tumor site							0.010[c]
Superior	50	19.3%	18	36.0%	32	64.0%	
Mid	109	42.1%	14	12.8%	95	87.2%	
Inferior	34	13.1%	3	8.8%	31	91.2%	
Isthumus	9	3.5%	2	22.2%	7	77.8%	
Mid and Superior	30	11.6%	6	20.0%	24	80.0%	
Mid and Inferior	27	10.4%	3	11.1%	24	88.9%	
Visible ETE							0.091[c]
No	242	93.4%	40	16.5%	202	83.5%	
Yes	17	6.6%	6	35.3%	11	64.7%	
Subtype							1.000[c]
Conventional	256	98.8%	46	18.0%	210	82.0%	
Follicular variant	3	1.2%	0	0.0%	3	100.0%	
pT classification							0.089[c]
T1a	242	93.4%	40	16.5%	202	83.5%	
T3	9	3.5%	3	33.3%	6	66.7%	
T4	8	3.1%	3	37.5%	5	62.5%	
Positive nodes in Level VI							
Mean ± SD	0.71 ± 1.57		2.27 ± 2.68		0.44 ± 1.09		0.004[b]
No	183	70.7%	20	10.9%	163	89.1%	<0.001[a]
Yes	76	29.3%	26	34.2%	50	65.8%	
No. of removed nodes in Level VI							
Mean ± SD	4.17 ± 3.48		4.05 ± 3.08		4.19 ± 3.55		0.842[b]
ENE in level VI							
No	243	93.8%	34	14.0%	209	86.0%	<0.001[c]
Yes	16	6.2%	12	75.0%	4	25.0%	
HT							0.704[a]
No	200	77.2%	37	18.5%	163	81.5%	
Yes	59	22.8%	9	15.3%	50	84.7%	

Abbreviations: PTC, papillary thyroid carcinoma; LNM, lateral neck metastasis; SD, standard deviation; ETE, extrathyroidal extension; TSH, thyroid-stimulating hormone; ENE, extranodal extension; HT, Hashimoto thyroiditis.
[a] Pearson's chi-square test.
[b] Student's *t*-test.
[c] Fisher's exact test.

Only clinical variables were included to generate a clinical model. After stepwise model selection, four variables were integrated into a final clinical model: age, ETE, tumor size, and lesions of the superior portion. Both clinical and pathological variables were considered to generate a clinicopathological model. After selection, four variables showed independent association with the risk of LNM and thus were integrated: tumor size, lesions of the superior portion, number of positive nodes in level VI, and ENE in level VI (Table 3).

Finally, two predictive nomograms were generated: nomogram (c) and nomogram (c + p). Nomogram (c) was based on the final clinical model, whereas nomogram (c + p) was based on the final clinicopathological model (Fig. 1). These two nomograms could help estimate the metastasis risk of lateral neck for individual patients with unifocal PTC. For example, nomogram (c + p) predicts that a PTC patient with a 30 mm tumor (37 points) located in the middle and inferior portion (2 points), without positive nodes in level VI (0 point), and without ENE (0 point), has a lower than 30% chance (total points, 39) of LNM. Conversely, a patient with a 10 mm lesion (12 points) located in the superior thyroid pole (31 points), with two positive nodes in level VI (14 points), and with ENE (38 points), has a more than 90% risk (total points, 95) of LNM.

Nomogram (c) had a good discriminative ability (C-index, 0.79; bootstrap-corrected, 0.78), whereas nomogram (c + p) had an excellent discriminative ability (C-index, 0.86; bootstrap-corrected, 0.85). Two nomograms were further internally calibrated using a similar bootstrap resampling procedure (Fig. 2). Predicted and observed metastasis risks of lateral neck were in good agreement; after adjustment for optimism, the corrected risks also showed excellent agreement with observed metastasis risks, and only minor discrepancies were observed.

By analyzing the data of 399 patients with cN0 lateral neck, another two nomograms were generated to predict the metastatic risk for cN0 lateral neck patients (for details, see Supplemental Fig. S1 and Supplemental Fig. S2).

Discussion

Lymph node metastasis is very common in PTC patients [3]. Besides the central compartment, the lateral neck is regarded as the second most common region that is involved [1,3]. Lateral neck metastasis occurs in 25%–65% of PTC patients [2–6]. The lateral neck contains levels II through V [8]. Among these, levels IIa, III, and IV are more commonly involved than level IIb and V [1,13].

Little controversy exists about therapeutic LND, which is recommended to treat patients with biopsy-proven metastatic nodes in the lateral neck [7]. However, much controversy exists about prophylactic LND, which is recommended to patients with clinically negative lateral neck (cN0) [5,7,8,14,15]. First, opponents assume that prophylactic LND increases operating time and results in more postoperative morbidities [16], such as chyle leak, spinal accessory nerve dysfunction, neck seroma; second, prophylactic LND has no obvious survival benefits for patients [8]; third, nodal status in the lateral neck can be accurately assessed by preoperative ultrasound examination [17,18]. Patients who are diagnosed as cN0 have little possibility of LNM. Fourth, even if lateral neck recurrence/persistence is observed during follow-up, the metastatic lymph nodes progress so slowly due to the indolent nature of PTC that they can be easily removed during reoperations.

However, those who advocate prophylactic LND assume that PTC is a lymphotropic disease, and the incidence of lateral neck metastasis is high enough to deserve close clinical attention [1,19,20]. Second, although ultrasound assessment is routinely performed to distinguish different nodal status, it is still a

Table 3
Univariate and multivariate logistic regression analysis for predicting lateral neck metastasis in 505 patients with unifocal PTC.

	Univariate Model			Final Multivariate Models					
				Clinical Model[a]			Clinicopathological Model		
	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	p value
Gender									
Female	1.00								
Male	1.09	0.72 to 1.63	0.676						
Age (years)	0.98	0.96 to 0.99	0.002	0.99	0.99 to 0.99	0.001			
Primary tumor size (mm)	1.09	1.07 to 1.12	<0.001	1.02	1.01 to 1.02	<0.001	1.08	1.05 to 1.11	<0.001
Side									
Right	1.00								
Left	0.78	0.53 to 1.13	0.192						
Isthmus	0.27	0.04 to 1.01	0.090						
Tumor site									
Inferior	1.00			1.00			1.00		
Mid	0.92	0.49 to 1.77	0.799	1.02	0.90 to 1.15	0.769	1.29	0.58 to 3.00	0.538
Isthmus	0.45	0.07 to 1.88	0.330	0.92	0.72 to 1.18	0.511	0.93	0.13 to 4.49	0.938
Superior	2.78	1.44 to 5.52	0.003	1.31	1.14 to 1.49	<0.001	5.67	2.49 to 13.69	<0.001
Mid and Superior	1.99	0.96 to 4.19	0.067	1.13	0.97 to 1.30	0.111	2.41	0.96 to 6.21	0.065
Mid and Inferior	1.17	0.54 to 2.54	0.696	0.99	0.86 to 1.16	0.999	1.05	0.39 to 2.84	0.923
Whole Lobe	23.14	5.88 to 155.48	<0.001	0.95	0.73 to 1.24	0.707	2.32	0.40 to 19.64	0.383
Visible ETE									
No	1.00			1.00					
Yes	3.36	2.15 to 5.30	<0.001	1.14	1.02 to 1.26	0.016			
pT classification									
T1a	1.00								
T1b	4.06	2.43 to 6.83	<0.001						
T2	7.19	3.75 to 14.05	<0.001						
T3	5.74	3.14 to 10.63	<0.001						
T4	11.10	5.60 to 22.97	<0.001						
Preoperative TSH level (mIU/L)	1.00	0.99 to 1.01	0.817						
No. of positive nodes in Level VI	1.76	1.55 to 2.03	<0.001				1.51	1.30 to 1.77	<0.001
ENE in level VI									
No	1.00						1.00		
Yes	20.82	10.55 to 46.08	<0.001				9.19	4.23 to 21.91	<0.001
HT									
No	1.00								
Yes	0.93	0.59 to 1.44	0.741						

Abbreviations: PTC, papillary thyroid carcinoma; CI, confidence interval; ETE, extrathyroidal extension; TSH, thyroid-stimulating hormone; ENE, extranodal extension; HT, Hashimoto thyroiditis.
[a] Only clinical variables were included into the final clinical mod.

subjective examination and relies highly on the operator's experience [21]. The sensitivity of ultrasound is poor, as low as 27%, which may lead to false stage assignment [4,9]. The diagnostic accuracy in low-volume institutions decreases dramatically, which makes the results less valuable. Third, some recent papers have claimed that the existence of metastatic lymph nodes is associated with compromised prognosis [6,22,23]. Fourth, long-term complications are uncommon if operations are performed by skilled surgeons [16,24]. Prophylactic, selective LND of levels III and IV may bring fewer postoperative complications [5]. Fifth, prophylactic LND can reduce the incidence of recurrence/persistence as well as following reoperations [6,14,23,25–28]. It may also reduce the incidence of isolated thyroglobulinemia as well as the need for repeated radioiodine treatments [9]. Sixth, prophylactic LND can provide precise lymph node staging and inform the use of radioiodine ablation [9].

The newly issued American Thyroid Association (ATA) guidelines recommend ultrasound-guided fine-needle aspiration biopsy (FNAB) for sonographically suspicious lymph nodes >8–10 mm in the smallest diameter (recommendation 32) [7]; the guidelines also recommend therapeutic LND for patients with biopsy-proven metastatic lateral cervical lymphadenopathy (recommendation 37) [7].

Only pathological results of ultrasound-guided FNAB are considered in the ATA guidelines when making a decision about LND. However, ultrasound-guided FNAB is not available in many institutions, and the accuracy relies highly on the experience of US operators and pathologists [29]. Another limitation of FNAB is the indefinite results due to inadequate/insufficient samples or indeterminate cytological patterns [30]. On the other hand, no recommendations are provided to patients with suspicious lymph nodes <8–10 mm in the smallest diameter or with occult lymph node metastases.

Many clinicopathological factors associated with LNM have been reported, including tumor size [14,31], central nodal metastasis [1,26,28,31–37], aggressive histological variants [26], superior location [35,38], extrathyroidal extension [35], and multifocal lesions [35]. However, none of these factors were considered in the new ATA guidelines to help stratify PTC patients and tailor LND.

Similar results were obtained in our study (Tables 2 and 3). After stepwise multivariate logistic regression analysis, two factors were found independently associated with LNM, in both the final models: tumor size and superior lesions. Age and visible ETE also showed an independent association in the final clinical model, whereas number of positive nodes in level VI and ENE in level VI showed a strong association in the final clinicopathological model. In details, when the other variables were fixed in the clinicopathological model, each increase in tumor size by 1 mm was associated with a 1.08-fold (95% confidence interval [CI], 1.05 to 1.11) higher risk of LNM, and each increase by one positive node in level VI was associated with a 1.51-fold (95% CI, 1.30 to 1.77) higher risk of LNM. Similarly, patients with ENE in level VI had a 9.19-fold (95% CI, 4.23 to 21.91) higher risk than those without ENE, and patients with a

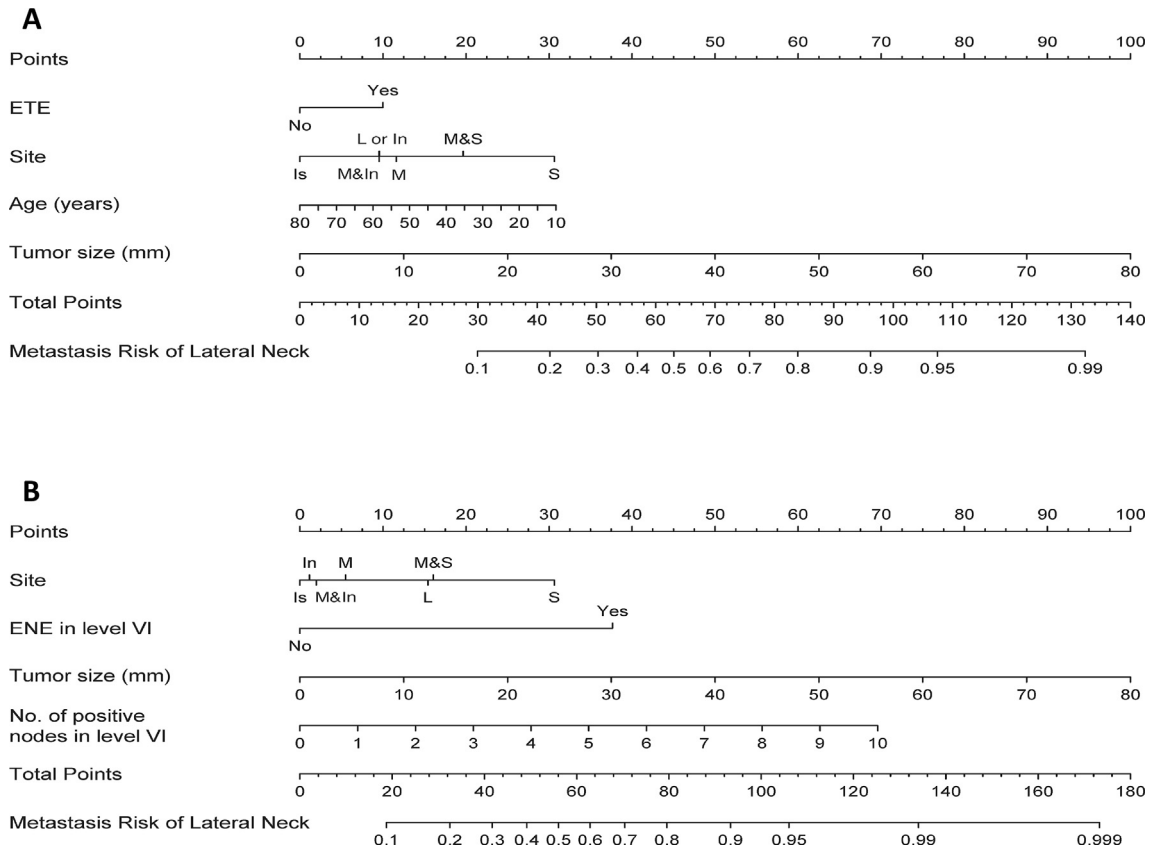

Fig. 1. Nomograms for predicting the probability of lateral neck metastasis in patients with unifocal papillary thyroid carcinoma. (A) Clinical model; (B) Clinicopathological model. To assess metastasis risk, draw a vertical line from each variable axis to the "Points" axis. Sum all points together and locate this sum on the "Total Point" axis. Then draw a vertical line from the "Total Points" axis to the axis labeled "Metastasis Risk of Lateral Neck" to find patient probability.
Abbreviations: S, superior third; M, middle third; In, inferior third; Is, isthmus; M&In, middle and inferior; M&S, middle and superior; L, whole lobe.

superior lesion had a 5.67-fold (95% CI, 2.49 to 13.69) higher risk than those with an inferior lesion.

The nomogram can incorporate all these factors, generate an individual probability of a clinical event, and finally aid clinicians in decision making [39]. However, no such nomogram has been established to predict LNM risk in PTC patients. This study summarized our data and first built two predictive nomograms based on predictors identified in the multivariate regression models (Fig. 1). Both nomograms showed a perfect discriminative ability, with a C-index of 0.79 and 0.86, respectively.

A risk stratification scheme is also proposed based on the predictive nomogram (c) (Table 4). This scheme stratifies PTC patients into low-, intermediate-, and high-risk groups (for details, see Supplemental Fig. S3). It also provides different treatment options. Prophylactic LND is not recommended for low-risk patients with a nomogram score between 0 and 0.30; prophylactic LND is highly recommended for high-risk patients with a nomogram score between 0.61 and 1.0; and prophylactic LND can be considered for patients in the intermediate-risk group with a nomogram score between 0.31 and 0.60.

In the dispute regarding the role of prophylactic LND in PTC patients, these nomograms provide an appropriate balance to avoid over-as well as under-treatment through individual risk estimation. Compared with ultrasound-guided FNAB, this nomogram provides another approach to helping decision making. Prophylactic LND should be performed in PTC patients with a high probability of LNM to reduce the incidence of reoperations due to lateral neck recurrence; on the other hand, prophylactic LND should be avoided in patients with a low probability of LNM to reduce potential damage and surgical complications.

An added value of this study is related to the importance and clinical significance in assessing lymph node status in level VI [36]. Number of positive nodes and ENE in level VI were two independent factors to predict the probability of LNM. As has been recently stressed by other papers [40,41], we also propose intraoperative frozen section analysis of lymph nodes in level VI for facilitating LNM risk assessment. These nomograms are also useful in estimating and stratifying LNM risk in patients without LND during primary thyroid surgeries and help make different follow-up strategies [26].

In this study, all patients identified underwent either therapeutic or prophylactic LND. LND was also performed routinely in micro-PTC patients and the decision was based on the following concerns: first, the incidence of LNM was reported as high as 44.5% even in patients with microcarcinoma, although most of the metastatic lymph nodes might remain indolent and rarely become clinically significant [3]. Second, we assumed that tumor size alone was not enough to make an LND decision. Our study showed that other clinicopathological factors were also crucial in predicting LNM, such as age, ETE, tumor location, number of positive nodes in level VI, and ENE in level VI. All these factors should be considered comprehensively, and our nomograms could perfectly integrate them to help clinicians make a better decision.

Both nomograms make no reference to preoperative US scan, which is a subjective examination and is widely used in clinics to predict LNM. We assume that US scan integration will greatly affect the predictive capacity of nomograms due to operators with different levels of experience, and thus reduce the universal

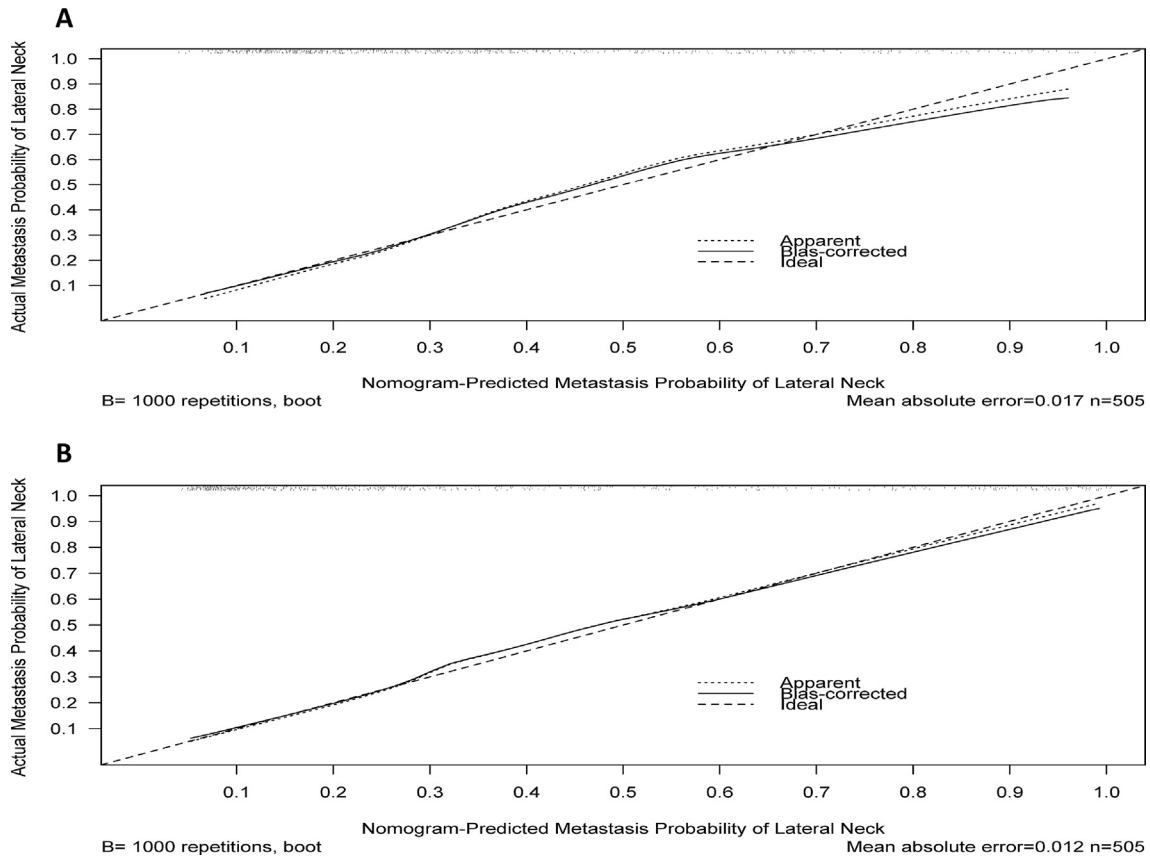

Fig. 2. Calibration plots for internal validation of the lateral neck metastasis nomograms. (A) Clinical model; (B) Clinicopathological model. x-axis is nomogram-predicted metastasis probability of lateral neck. y-axis is actual metastasis probability of lateral neck. Dashed line = ideal nomogram; dotted line = apparent predictive accuracy; solid line = calibration estimate from internally validated model.
Perfect prediction would correspond to the dashed line.

Table 4
Metastasis risk stratification and individualized treatment of patients with unifocal PTC based on risk scores of nomogram (c) model.

Total Points	Nomogram-based Risk Score	Metastasis Risk in Lateral Neck	LND
≤50	0 to 0.30	Low risk	No
51 to 69	0.31 to 0.60	Intermediate risk	Consider LND
≥70	0.61 to 1.0	High risk	Yes

Abbreviations: PTC, papillary thyroid carcinoma; LND, lateral neck dissection.

applicability of our nomograms. Our nomograms do not contradict the use of preoperative US scan. On the contrary, they may be a useful adjuvant to US scan, especially when PTC patients are examined by US operators with less experience.

Our nomograms have some limitations. First, this is a retrospective, single-institution study. A nomogram based on a prospective, multicenter study will be more powerful and more reproducible. Second, our models need further external validation by other institutions' data to assess potential overfitting. Third, among the four variables integrated into the nomogram (c + p), measurements of tumor site and tumor size were obtained by preoperative ultrasound assessment, whereas measurements of ENE and number of positive nodes in level VI were obtained by postsurgical histopathology. Although nomogram (c + p) cannot influence a decision preoperatively, it might help clinicians make an active follow-up strategy for patients in high-risk group. Fourth, no gene mutation data was considered in our models. Although some mutations may be associated with lymph node metastasis in PTC [42,43], further verification is needed to assess whether these mutations can be integrated with these nomograms. Fifth, although our nomograms may aid decision making regarding LND, whether undergoing LND is beneficial in terms of survival benefit for those who do not present with clinically involved nodes is still controversial. This issue is outside the scope of our study.

We have built two nomograms to predict LNM risk in patients with unifocal PTC. Each nomogram incorporates either four clinical or four clinicopathological factors and represents a user-friendly tool to give an accurate estimation for each patient. We also propose a risk stratification scheme as well as corresponding surgical approaches based on different nomogram scores.

Declaration of conflicts of interest

None.

Acknowledgements

The authors acknowledge the financial support from Henan

Health Agency (Grant No. 201403211).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.02.016.

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