Ultrasound-Based Radiomics Analysis for Preoperative Prediction of Central and Lateral Cervical Lymph Node Metastasis in Papillary Thyroid Carcinoma: A Multi-Institutional Study

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Abstract

Background

An accurate preoperative assessment of cervical lymph node metastasis (LNM) is important for choosing optimal therapeutic strategy for papillary thyroid carcinoma (PTC) patients. This study aimed to develop and validate two ultrasound (US) nomograms for the individual prediction of central and lateral compartment LNM in patients with PTC.

Methods

A total of 720 PTC patients from 3 institutions were enrolled in this study. They were categorized into a primary cohort, an internal validation, and two external validation cohorts. Radiomics features were extracted from conventional US images. LASSO regression was used to select optimized features to construct the radiomics signature. Two nomograms integrating independent clinical variables and radiomics signature were established with multivariate logistic regression. The performance of the nomograms was assessed with regard to discrimination, calibration, and clinical usefulness.

Results

The radiomics scores were significantly higher in patients with central/lateral LNM. A radiomics nomogram indicated good discrimination for central compartment LNM, with an area under the curve (AUC) of 0.875 in the training set, the corresponding value in the validation sets were 0.856, 0.870 and 0.870, respectively. Another nomogram for predicting lateral LNM also demonstrated good performance with a training AUC of 0.938, an internal validation AUC of 0.905, and two external validation AUC of 0.881 and 0.903, respectively. The clinical utility of the nomograms was confirmed by the decision curve analysis.

Conclusion

The nomograms proposed here have favorable performance for preoperatively predicting cervical LNM, and hold promise for optimizing the personalized treatment, which may improve the survival outcome in PTC patients.

Introduction

Papillary thyroid carcinoma (PTC) accounts for approximately 85% of all thyroid carcinoma cases, and its global incidence is increasing over the past few decades(1). Despite having an indolent clinical course, PTC is associated with cervical lymph node metastasis (LNM)(2). Cervical LNM occurs in approximately 30-80% of PTC cases and is one of the most important risk factors for locoregional recurrence(3). The

presence of LNM also affects the staging and treatment options for PTC(4). Central compartment LNM is usually treated with central compartment neck dissection (CCND), and central LNM has been found in 45% of PTC patients with clinically negative LNs (cN0) who undergo prophylactic CCND(5). However, the risk of hypoparathyroidism and recurrent laryngeal nerve injury is heightened with CCND, whether CCND should be performed prophylactically in cN0 patients remains controversial(6). Patients with preoperatively evident lateral nodal metastasis typically require aggressive treatment, including lateral compartment lymph node (LN) dissection and high-dose radioactive iodine (RAI) therapy(7). However, therapeutic neck dissection and/or RAI ablation increases the morbidity and reduces the quality of life(8). The reduction of the incidence of complication must be based on reduction of unnecessary CLN dissection. Therefore, an accurate preoperative assessment of cervical LNM is important for choosing the optimal therapeutic strategy for PTC patients.

Ultrasound (US) is the preferred screening modality for preoperative assessment of cervical LN (CLN) status in PTC patients(9). However, preoperative US has a low sensitivity (38-59%) for detecting cervical LNM(6, 10). Furthermore, the diagnostic performance of neck US differs among physicians and the interobserver variability is high(11). Fine-needle aspiration (FNA) is an invasive approach and its sensitivity in evaluating LNM varies and is specific to operator(12). Thus, a non-invasive, effective alternative imaging modality with improved accuracy is urgently needed in clinical practice.

Fueled by the rapid advances in medical imaging and developments in analytical methods, the field of radiomics has attracted increasing research attention in recent years(13). Radiomics refers to the high-throughput extraction of extensive quantitative features to convert medical images into mineable data that could likely be used as diagnostic, predictive or prognostic biomarkers and support the clinical decision-making system(14). Accordingly, our previous studies have proved the value of radiomics in predicting the cervical LNM of PTC(15–17). To our knowledge, the US radiomics method applied in individually predicting cervical central and lateral LNM for PTC patients, respectively, has not been reported yet.

Therefore, the current study aimed to develop and validate nomograms which incorporated the US radiomics as well as the clinical risk factors for individual prediction of central and lateral cervical LNM in PTC patients.

Materials And Methods

Patients

Between January 2019 to June 2019, consecutive patients with thyroid nodules in hospital 1 (Fudan University Shanghai Cancer Center, Shanghai, China; training and validation cohort 1), hospital 2 (Zhongshan Hospital, Fudan University, Shanghai, China; validation cohort 2) and hospital 3 (Ruijin Hospital, Shanghai Jiao Tong University, Shanghai, China; validation cohort 3) were included. The inclusion criteria were as follows: (X) primary surgical resection was performed for the target tumor which had a pathological diagnosis of PTC; (X) preoperative neck US was performed, and the images were

recorded and saved as DICOM format; (X) US images meet the requirements for the stored images(15); (X) patients with complete clinicopathological information. The exclusion criteria included the following: (X) patients with more than one lesion confirmed to be PTC; (X) no history of preoperative therapy (radiofrequency or microwave ablation, neck radiation therapy); (X) patients with only microscopic cervical LNM. After that, a total of 720 patients were enrolled in this study. Four hundred forty-three patients were chronologically divided into two cohorts: the training cohort with 300 patients who were treated between January and April 2019, and the internal validation cohort with 143 patients who were treated between May and June 2019. Two external validation cohorts of 144 and 133 consecutive patients, respectively, were included using the same criteria. The patients were divided into two groups based on the pathological reports of the lymph node status after CLN dissection.

This retrospective study was approved by the Ethics Committees of all participating hospitals (Shanghai Cancer Center, Ruijin Hospital, and Zhongshan Hospital), and performed in accordance with the Declaration of Helsinki. The inform consent was waived because of the retrospective nature of the study.

Surgery and Pathology

All patients received either total thyroidectomy or lobectomy in accordance with the clinical TNM staging, and underwent therapeutic or prophylactic central compartment dissection. Lateral neck LN dissection was performed for patients with FNA proven, or radiologically suspicious LNs that were not suitable for FNA. The resected thyroid and LNs specimen were collected and subjected to pathological examination, including the determination of unifocal or multifocal, and tumor size (maximum diameter of the tumor); the number, size and neck level of the metastatic LNs. The pathological results of the LNs were used as the gold standard(15).

Clinical characteristics

The baseline clinical information, including age, gender, thyroglobulin (TG), thyroid stimulating hormone (TSH), thyroglobulin antibody (TGAB), thyroid peroxidase antibody (TPOAB), and cytological findings of FNA were collected from the medical record system. The results of TG, TSH, TGAB, and TPOAB were detected within one week prior to surgical treatment. According to the previous reports and clinical experience(18, 19), the threshold set for TG, TSH, TGAB, and TPOAB were as follows: $TG \geq 77$ ng/ml, $TSH \geq 2.5$ ng/ml, $TGAB \geq 100$ IU/ml, and $TPOAB \geq 35$ IU/ml. Imaging data including US images, US reports and CT reports were obtained from medical image station.

US image acquisition and US-reported CLNs status

All patients received neck US examination before surgery. US images were acquired with a Supersonic Aixplorer System using a 15-4 linear-array transducer (SuperSonic Imaging, France) by radiologists with more than 6 years of experience. The US acquisition parameters were consistent among patients: image depth, 3cm; focus parallel to the lesion, and gain 53%, and the spatial resolution of axial and lateral was 0.2 mm and 0.4 mm, respectively(20). The detailed requirements for the US images were described in our

previous study(20). The diagnostic result “central LNM” or “lateral LNM” in the US report was defined as US-reported central/lateral cervical LNM positive. The results of “LNs negative”, “inflammatory LNs” and “small LNs” were categorized as US-reported central/lateral cervical LNM negative(15, 20). The abnormal US finding suggestive of LNM include the following: (x) round shape; (x)absence of the fatty hilum; (x) microcalcification within the nodes; (x) presence of peripheral flow; (v) heterogeneity with cystic components(21). LNs that met two or more of the five criteria would be considered positive. The diagnostic sensitivity, specificity and accuracy of neck US examination in the training and validation sets were calculated based upon the US reports(15).

Region of interest segmentation and feature extraction

A representative US image were selected, in which the tumor was manually segmented by 2 senior US physicians with more than 6-year-experience in thyroid US imaging who were blinded from the final LNs status. The MATLAB software written by our team was used to extract radiomics features (MATLAB R2015b, Mathworks). To evaluate the reproducibility of feature extraction, fifty cases were randomly selected and double-blinded for comparing manual segmentation by two physicians. The interclass correlation coefficient (ICC) was calculated to measure the intra-observer and inter-observer agreement of the radiomics feature extraction. An ICC greater than 0.80 was considered to indicated good agreement.

Feature selection, radiomics signature building, and validation

The detailed procedure of radiomics feature selection was described in our previous study(15). The selected radiomics features were then combined to build a radiomics signature. Based on the estimated coefficient, a radiomics score (Rad-score) for each case was computed to reflect the risk of cervical central and lateral LNM. The association between US radiomics signature and central/lateral LNs status was assessed in the training cohort by Mann-Whitney U test before being subjected to the validation cohorts.

Development of US radiomics nomogram

Student’s t test (continuous variables) or χ^2 test (categorical variables) was employed to identified the clinicopathological factors associated with central and lateral cervical LNM. A multivariate logistic regression analysis comprising the Rad-score and the independent risk factors was conducted. The backward stepwise selection procedure was utilized with a liberal p value less than 0.05 as the retention criteria to select the final independent predictors for central/lateral LNM. Then a radiomics nomogram was developed based on the multivariate analysis in the training set.

Performance of the US radiomics nomogram

The receiver operating characteristic curve (ROC) of the US-reported LN status, radiomics signature, and radiomics nomogram in each cohort was plotted. The discriminatory performance of the three models was evaluated using the area under curve (AUC). Calibration of the US radiomics nomogram in all four

cohorts was assessed by the calibration curve and Hosmer-Lemeshow test. To determine the clinical usefulness of the US radiomics nomogram, decision curve analysis (DCA) was performed by quantifying the net benefits at different threshold probabilities in our entire dataset.

Statistical analysis

The statistical analyses were performed with R software (version 3.5.3 <http://www.r-project.org>), where the package 'shiny', 'foreign', 'nomogramFormula', 'tmcn', 'rms', 'set', 'glmnet', 'rmda' and 'DT' were applied. All other statistical tests were conducted using SPSS software (version 26, Chicago, IL). The categorical and continuous variables were presented as frequency (percentage) and mean $\pm$ standard deviation (SD), respectively. Categorical variables were compared by χ^2 test; student's t-test was used for comparison between continuous variables. The Delong test was employed to compare different AUC. A two-sided $p < 0.05$ was considered to indicate statistically significant.

Results

Clinical characteristics

The clinicopathological characteristics of the patients in the entire dataset were presented in Table 1 and 2. The positive rate in terms of the central LNM in the training and validation cohorts were 34.7%, 32.9%, 48.6%, and 31.6%, respectively; and 9.0%, 10.5%, 10.4%, and 14.3%, respectively, with regard to the lateral LNM. No significant differences in the positive rate were found among the four cohorts ($p=0.058$; $p=0.435$).

Table 1
Associations between the central CLN status and clinical parameters in the training and validation cohorts

Training cohort (n=300)			Validation cohort 1 (n=143)			
Characteristic	CLNM + (n=104)	CLNM – (n=196)	<i>p</i>	CLNM + (n=47)	CLNM – (n=96)	<i>p</i>
Age (years)			<0.001			0.038
Mean ± SD	38.9 ± 10.6	45.3 ± 11.4		39.0 ± 11.4	43.6 ± 12.6	
Age (years)			<0.001			0.011
>45	28 (26.9)	94 (48.0)		13 (27.7)	48 (50.0)	
≤45	76 (73.1)	102 (52.0)		34 (72.3)	48 (50.0)	
Gender (%)			0.623			0.157
Male	32 (30.8)	55 (28.1)		16 (34.0)	22 (22.9)	
Female	72 (69.2)	141 (71.9)		31 (66.0)	74 (77.1)	
TSH (%)			0.487			0.975
Normal	93 (89.4)	180 (91.8)		44 (93.6)	90 (93.8)	
Abnormal	11 (10.6)	16 (8.2)		3 (6.4)	6 (6.3)	
TG (%)			0.143			0.482
Normal	92 (88.5)	183 (93.4)		45 (95.7)	89 (92.7)	
Abnormal	12 (11.5)	13 (6.6)		2 (4.3)	7 (7.2)	
TGAB (%)			0.518			0.111
Normal	64 (61.5)	128 (65.3)		27 (57.4)	68 (70.8)	
Abnormal	40 (38.5)	68 (34.7)		20 (42.6)	28 (29.2)	
TPOAB (%)			0.091			0.102
Normal	69 (66.3)	148 (75.5)		42 (89.4)	75 (78.1)	
Abnormal	35 (33.7)	48 (24.5)		5 (10.6)	21 (21.9)	
Tumor size (mm)			<0.001			<0.001

CLN, cervical lymph node; CLNM, cervical lymph metastasis; TG, thyroglobulin; TGAB, thyroglobulin antibody; TPOAB, thyroid peroxidase antibody; TSH, thyroid stimulating hormone; LNM, lymph node metastasis; SD, standard deviation; US, ultrasound. Significant differences are highlighted in boldface.

Training cohort (n=300)			Validation cohort 1 (n=143)		
Mean ± SD	13.4 ± 8.1	9.2 ± 5.9	13.9 ± 10.1	9.0 ± 7.6	
Tumor size (mm)	<0.001		<0.001		
≥1	64 (61.5)	53 (27.0)	29 (61.7)	15 (15.6)	
<1	40 (38.5)	143 (73.0)	18 (38.3)	81 (84.4)	
US-reported central CLN status (%)	<0.001		<0.001		
negative	52 (50.0)	177 (90.3)	24 (51.1)	87 (90.6)	
positive	52 (50.0)	19 (9.7)	23 (48.9)	9 (9.4)	
Radiomics score	-0.2873	-0.4266	<0.001	-0.2631	-0.4063
Median					
(interquartile range)	(-0.4481, -0.1983)	(-0.5547, -0.3014)	(-0.4026, -0.1533)	(-0.5130, -0.2765)	
	Validation cohort 2 (n=144)		Validation cohort 3 (n=133)		
Characteristic	CLNM + (n=70)	CLNM – (n=74)	<i>p</i>	CLNM + (n=42)	CLNM – (n=91)
Age (years)	0.017		0.014		
Mean ± SD	37.3 ± 10.9	41.9 ± 11.9	36.7 ± 12.1	45.2 ± 11.8	
Age (years)	0.052		0.018		
>45	22 (31.4)	35 (47.3)	12 (28.6)	46 (50.5)	
≤45	48 (68.6)	39 (52.7)	30 (71.4)	45 (49.5)	
Gender (%)	0.336		0.897		
Male	20 (28.6)	16 (21.6)	12 (28.6)	27 (29.7)	
Female	50 (71.4)	58 (78.4)	30 (71.4)	64 (70.3)	
TSH (%)	0.920		0.551		
Normal	64 (91.4)	68 (91.9)	38 (90.5)	85 (93.4)	

CLN, cervical lymph node; CLNM, cervical lymph metastasis; TG, thyroglobulin; TGAB, thyroglobulin antibody; TPOAB, thyroid peroxidase antibody; TSH, thyroid stimulating hormone; LNM, lymph node metastasis; SD, standard deviation; US, ultrasound. Significant differences are highlighted in boldface.

	Training cohort (n=300)		Validation cohort 1 (n=143)	
Abnormal	6 (8.6)	6 (8.1)	4 (9.5)	6 (6.6)
TG (%)			0.095	0.335
Normal	44 (62.9)	56 (75.7)	27 (64.3)	66 (72.5)
Abnormal	26 (37.1)	18 (24.3)	15 (35.7)	25 (27.5)
TGAB (%)			0.143	0.596
Normal	40 (57.1)	51 (68.9)	32 (76.2)	73 (80.2)
Abnormal	30 (42.9)	23 (31.1)	10 (23.8)	18 (19.8)
TPOAB (%)			0.341	0.863
Normal	48 (68.6)	56 (75.7)	36 (85.7)	79 (86.8)
Abnormal	22 (31.4)	18 (24.3)	6 (14.3)	12 (13.2)
Tumor size (mm)			<0.001	<0.001
Mean ± SD	14.9 ± 7.1	8.3 ± 7.0	14.0 ± 11.2	8.3 ± 7.9
Tumor size (mm)			<0.001	0.001
≥1	41 (58.6)	20 (27.0)	33 (78.6)	20 (22.0)
<1	29 (41.4)	54 (73.0)	9 (21.4)	71 (78.0)
US-reported central CLN status (%)			<0.001	<0.001
negative	38 (54.3)	68 (91.9)	20 (47.6)	78 (85.7)
positive	32 (45.7)	6 (8.1)	22 (52.4)	13 (14.3)
Radiomics score			<0.001	<0.001
Median	-0.2431	-0.4058	-0.2695	-0.4438
(interquartile range)	(-0.3553, -0.1270)	(-0.5119, -0.3104)	(-0.3652, -0.1542)	(-0.5602, -0.3217)
CLN, cervical lymph node; CLNM, cervical lymph metastasis; TG, thyroglobulin; TGAB, thyroglobulin antibody; TPOAB, thyroid peroxidase antibody; TSH, thyroid stimulating hormone; LNM, lymph node metastasis; SD, standard deviation; US, ultrasound. Significant differences are highlighted in boldface.				

Table 2

Associations between the lateral CLN status and clinical parameters in the training and validation cohorts

Training cohort (n=300)				Validation cohort 1 (n=143)		
Characteristic	LLNM + (n=27)	LLNM – (n=273)	<i>p</i>	LLNM + (n=15)	LLNM – (n=128)	<i>p</i>
Age (years)			0.515			0.543
Mean ± SD	40.1 ± 10.9	42.6 ± 12.0		41.5 ± 16.9	43.5 ± 11.0	
Age (years)			0.221			0.440
>45	8 (29.6)	114 (41.8)		5 (33.3)	56 (43.8)	
≤45	19 (70.4)	159 (58.2)		10 (66.7)	72 (56.2)	
Gender (%)			0.159			0.542
Male	11 (40.7)	76 (27.8)		3 (20.0)	35 (27.3)	
Female	16 (59.3)	197 (72.2)		12 (80.0)	93 (72.7)	
TSH (%)			0.762			0.950
Normal	25 (92.6)	248 (90.8)		14 (93.3)	120 (93.8)	
Abnormal	2 (7.4)	25 (9.2)		1 (6.7)	8 (6.3)	
TG (%)			0.001			0.054
Normal	20 (74.1)	255 (93.4)		12 (80.0)	122 (95.3)	
Abnormal	7 (25.9)	18 (6.6)		3 (20.0)	6 (4.7)	
TGAB (%)			0.338			0.984
Normal	15 (55.6)	177 (64.8)		10 (66.7)	85 (66.4)	
Abnormal	12 (44.4)	96 (35.2)		5 (33.3)	43 (33.6)	
TPOAB (%)			0.254			0.847
Normal	17 (63.0)	200 (73.3)		12 (80.0)	105 (82.0)	
Abnormal	10 (37.0)	73 (26.7)		3 (20.0)	23 (18.0)	
Tumor size (mm)			<0.001			<0.001

CLN, cervical lymph node; CLNM, cervical lymph metastasis; TG, thyroglobulin; TGAB, thyroglobulin antibody; TPOAB, thyroid peroxidase antibody; TSH, thyroid stimulating hormone; LNM, lymph node metastasis; SD, standard deviation; US, ultrasound. Significant differences are highlighted in boldface.

Training cohort (n=300)			Validation cohort 1 (n=143)		
Mean ± SD	15.1 ± 6.9	9.0 ± 6.8	16.1 ± 11.7	8.8 ± 6.7	
Tumor size (mm)	<0.001		<0.001		
≥1	23 (85.2)	94 (34.4)	11 (73.3)	33 (25.8)	
<1	4 (14.8)	179 (65.6)	4 (26.7)	95 (74.2)	
US-reported lateral CLN status (%)	<0.001		<0.001		
negative	7 (25.9)	243 (89.0)	4 (26.7)	116 (90.6)	
positive	20 (74.1)	30 (11.0)	11 (73.3)	12 (9.4)	
Radiomics score	-0.0318	-0.1346	<0.001	-0.0590	-0.1414
Mean					<0.001
(interquartile range)	(-0.1413, -0.0081)	(-0.1706, -0.1114)	(-0.1357, -0.0323)	(-0.1973, 0.0986)	
Validation cohort 2 (n=144)			Validation cohort 3 (n=133)		
Characteristic	LLNM + (n=15)	LLNM – (n=129)	<i>p</i>	LLNM + (n=19)	LLNM – (n=114)
Age (years)	0.992		0.007		
Mean ± SD	39.7 ± 14.1	39.7 ± 11.4	38.8 ± 10.7	44.3 ± 12.3	
Age (years)	0.553		0.521		
>45	7 (46.7)	50 (38.8)	7 (36.8)	51 (44.7)	
≤45	8 (53.3)	79 (61.2)	12 (63.2)	63 (55.3)	
Gender (%)	0.270		0.816		
Male	2 (13.3)	34 (26.4)	6 (28.9)	33 (31.6)	
Female	13 (86.7)	95 (73.6)	13 (71.1)	81 (68.4)	
TSH (%)	0.459		0.154		
Normal	13 (86.7)	119 (92.2)	16 (84.2)	107 (93.9)	

CLN, cervical lymph node; CLNM, cervical lymph metastasis; TG, thyroglobulin; TGAB, thyroglobulin antibody; TPOAB, thyroid peroxidase antibody; TSH, thyroid stimulating hormone; LNM, lymph node metastasis; SD, standard deviation; US, ultrasound. Significant differences are highlighted in boldface.

	Training cohort (n=300)		Validation cohort 1 (n=143)	
Abnormal	2 (13.3)	10 (7.8)	3 (15.8)	7 (6.1)
TG (%)		0.730		0.487
Normal	11 (73.3)	89 (69.0)	12 (63.2)	81 (71.1)
Abnormal	4 (26.7)	40 (31.0)	7 (36.8)	33 (28.9)
TGAB (%)		0.161		0.224
Normal	7 (46.7)	84 (65.1)	17 (89.5)	88 (77.2)
Abnormal	8 (53.3)	45 (34.9)	2 (10.5)	26 (22.8)
TPOAB (%)		0.084		0.679
Normal	8 (53.3)	96 (74.4)	17 (89.5)	98 (86.0)
Abnormal	7 (46.7)	33 (25.6)	2 (10.5)	16 (14.0)
Tumor size (mm)		<0.001		<0.001
Mean ± SD	14.9 ± 7.1	8.3 ± 7.0	15.7 ± 7.2	8.5 ± 6.9
Tumor size (mm)		0.002		0.001
≥1	12 (80.0)	49 (38.0)	14 (73.7)	39 (34.2)
<1	3 (20.0)	80 (62.0)	5 (26.3)	75 (65.8)
US-reported lateral CLN status (%)		<0.001		<0.001
negative	4 (26.7)	112 (86.8)	5 (26.3)	99 (86.8)
positive	11 (73.3)	17 (13.2)	14 (73.7)	15 (13.2)
Radiomics score		<0.001		<0.001
Mean	-0.0629	-0.1501	-0.0496	-0.1345
(interquartile range)	(-0.1347, -0.0033)	(-0.2014, -0.1020)	(-0.1300, -0.0029)	(-0.1798, -0.1008)
CLN, cervical lymph node; CLNM, cervical lymph metastasis; TG, thyroglobulin; TGAB, thyroglobulin antibody; TPOAB, thyroid peroxidase antibody; TSH, thyroid stimulating hormone; LNM, lymph node metastasis; SD, standard deviation; US, ultrasound. Significant differences are highlighted in boldface.				

Feature Selection And Development Of The Us Radiomics Signatures

The procedure of feature extraction has been described in detail(16). Briefly, in the training set, 614 reproducible features were extracted from the original thyroid US images. Excellent intra- and inter-observer reproducibility of feature extraction was achieved, with intra-observer ICCs ranging from 0.823 to 0.932, and the inter-observer ICCs ranging from 0.841 to 0.954. The detailed procedures of the feature selection and the radiomics signature construction for predicting the central and lateral cervical LNM were described in our previous studies(15, 20), respectively.

Validation Of The Radiomics Signatures

The Rad-score were significantly higher in the central and lateral LNM groups in both the training set and the validation sets than that in the non-LNM groups ($p < 0.001$, $p < 0.001$, Table 1 and 2). The ROC curves were shown in figure 1 and 2. The radiomics signature yielded an AUC of 0.839 for discriminating between central/non-central LNM groups in the training set, and 0.819, 0.799, 0.797, respectively, in the validation sets 1, 2, and 3. The AUC for differentiating between lateral/non-lateral LNM groups was 0.908 in the training set, and were 0.888, 0.796, 0.793, respectively, in the validation cohorts 1, 2, and 3. The radiomics signatures yielded a better discriminatory performance than that of the US-reported LN status (Table 3 and 4).

Table 3

Diagnostic performance of US, radiomics signature, and nomogram in the training and validation cohorts

Cohorts	Sensitivity (%)	Specificity (%)	AUC (95%CI)	Accuracy (%)
US-reported central LN status in training cohort	50.0	90.3	0.702 (0.635-0.768)	76.3
Radiomics signature in training cohort	83.7	81.1	0.839 (0.792-0.887)	82.0
Radiomics nomogram in training cohort	83.7	81.6	0.875 (0.834-0.915)	82.3
US-reported central LN status in validation cohort 1	48.9	90.6	0.698 (0.599-0.797)	76.9
Radiomics signature in validation cohort 1	78.7	81.2	0.819 (0.738-0.900)	80.4
Radiomics nomogram in validation cohort 1	83.0	82.3	0.857 (0.785-0.929)	82.5
US-reported central LN status in validation cohort 2	45.7	91.9	0.688 (0.600-0.776)	69.4
Radiomics signature in validation cohort 2	65.7	79.7	0.799 (0.729-0.869)	72.9
Radiomics nomogram in validation cohort 2	77.1	85.1	0.880 (0.826-0.934)	81.3
US-reported central LN status in validation cohort 3	52.4	85.7	0.690 (0.587-0.794)	75.1
Radiomics signature in validation cohort 3	71.4	74.7	0.797 (0.716-0.879)	73.7
Radiomics nomogram in validation cohort 3	71.4	87.9	0.870 (0.808-0.932)	82.7
US, ultrasound; CT, computed tomography; AUC, area under curve; CI, confidence interval.				

Table 4

Diagnostic performance of US, radiomics signature, and nomogram in the training and validation cohorts

Cohorts	Sensitivity (%)	Specificity (%)	AUC (95%CI)	Accuracy (%)
US-reported lateral LN status in training cohort	74.1	89.0	0.815 (0.716-0.915)	87.6
Radiomics signature in training cohort	77.8	90.1	0.908 (0.845-0.972)	89.0
Radiomics nomogram in training cohort	81.5	94.1	0.938 (0.887-0.989)	93.0
US-reported lateral LN status in validation cohort	73.3	90.6	0.820 (0.684-0.955)	88.8
Radiomics signature in validation cohort 1	80.0	91.4	0.888 (0.786-0.990)	90.2
Radiomics nomogram in validation cohort 1	86.7	92.2	0.905 (0.789-0.999)	91.6
US-reported lateral LN status in validation cohort 2	73.3	86.8	0.801 (0.665-0.936)	85.4
Radiomics signature in validation cohort 2	66.7	82.9	0.796 (0.684-0.909)	84.7
Radiomics nomogram in validation cohort 2	73.3	93.0	0.884 (0.785-0.984)	90.9
US-reported lateral LN status in validation cohort 3	73.7	86.8	0.803 (0.681-0.924)	85.0
Radiomics signature in validation cohort 3	68.4	75.4	0.793 (0.683-0.903)	74.4
Radiomics nomogram in validation cohort 3	78.9	89.5	0.906 (0.841-0.971)	88.0
US, ultrasound; CT, computed tomography; AUC, area under curve; CI, confidence interval.				

Prediction Of Ln Status Based On Radiomics Nomogram

The age (<45), US-reported central CLN status, and radiomics signature were identified as independent predictive factors for central LNM; the US-reported lateral CLN status and radiomics signature were identified as independent variables for lateral LNM by multivariate logistic regression analysis (Table 5 and 6). The two radiomics nomograms were constructed by incorporating the independent predictors, respectively (Figure 3). In the training sets, the radiomics nomogram showed the highest discrimination between central LNM positive and negative with an AUC of 0.875 (95%CI, 0.834-0.915); the nomogram for discriminating between the lateral LNM positive and negative also yielded the greatest AUC (0.938,

95%CI: 0.887-0.989), which indicated that nomogram achieved better discriminatory performance than either the US-reported CLN status or the radiomics signature. The favorable discrimination was also observed in the validation cohorts (Table 3 and 4). Thus, our nomogram performed well in both the training cohort and the validation cohorts. The calibration curve of the radiomics nomograms for the probability of central/lateral LNM demonstrated an optimal consistency between prediction and pathologic observation in the training and validation cohorts (Figure 4 and 5). The Hosmer-Lemeshow test showed no statistical significance, which suggested no significant deviation from a perfect fit.

Table 5
Independent predictive factors for central LNM in the radiomics nomogram

Variables	β	Odds Ratio (95% CI)	p
Age	0.934	2.544 (1.317-4.913)	0.005
US-reported central CLN status	2.007	7.444 (3.597-15.406)	<0.001
US radiomics signature	6.354	574.537 (96.796-3410.181)	<0.001
Constant	0.473		0.225
CI, confidence interval; CLN indicates cervical lymph nodes; US, ultrasound.			

Table 6
Independent predictive factors for lateral LNM in the radiomics nomogram

Variables	β	Odds Ratio (95% CI)	p
US-reported central CLN status	25.752	142.012 (28.751-701.016)	<0.001
US radiomics signature	2.693	14.772 (4.312-50.607)	<0.001
Constant	-1.125		0.031
CI, confidence interval; CLN indicates cervical lymph nodes; US, ultrasound.			

Clinical Significance

The decision curve analyses (DCA) for the US-reported CLN status, the radiomics signature, and the nomograms are illustrated in figure 6. The DCA demonstrated that the nomogram exhibited an optimal net benefit to predict the central LNM than other models for threshold probability within the range of 0-0.98, and the prediction of lateral LNM with radiomics nomogram could benefit more as compared to the radiomics signature and the US-reported lateral CLN status when the threshold probability ranged from 0.04 to 0.98.

Discussion

In this study, we developed and validated two radiomics nomograms to improve the accuracy in preoperatively predicting the central and lateral LNM, respectively, in a non-invasive and individualized fashion. In this multi-institutional study, the two nomograms showed favorable predictive ability in both training and independent validation cohorts, outperforming the radiologists' subjective prediction of cervical LNM and the radiomics signature. Furthermore, the DCA also demonstrated that the nomograms had the best net benefit within a wide range of threshold probabilities. These results highlighted that our radiomics nomograms provided a new method for the preoperatively individualized prediction of central and lateral LNM in PTC patients. This approach might greatly facilitate the decision-making in the clinical practice.

Accurate preoperative predicting the cervical LNM of patients with PTC is of great importance for guiding clinical treatment, particularly, for surgeons to determine the extent of the surgical resection and assessing the necessity of CLN dissection(3, 13). Neck US examination plays a pivotal role in PTC staging. Unfortunately, the detection rate of cervical LNM is not desirable. Since US is unable to consistently visualize the deep anatomic structures, or structures which are acoustically shadowed by air and bone(22), in many patients, the LNM in the central compartment may not show any abnormal finding in preoperative US examination(23). Besides, US examination is an empirical diagnosis which is greatly affected by the expertise of the operator, therefore, prone to interobserver variability when determining lateral LNM(8). Many studies have investigated the association between cervical LNM and the morphologic US features of primary tumor, and have reported that the "taller than wide" shape, tumor size, presence of calcification, and closer distance between tumor and capsule were independent risk factors for LNM(15, 24–26). Although, the US features mentioned above are encouraging, the imaging features are also based on the judgement of the performing physician and thus, lack objectivity. However, utilizing imaging features of the primary tumor enables an approach which is less affected by the expertise of the operator, thus could be a promising tool for clinical practice(8).

Radiomics is a novel method, which extracts high-throughput quantitative information from standard-of-care medical imaging that improves medical decision-making, has drawn increased attention in cancer research(27, 28). Currently, radiomics has been explored in the field of thyroid carcinoma research, such as in the differential diagnosis of thyroid nodules(29), prediction of the cervical LNM(16), extrathyroidal extension(30), BRAF^{V600E} mutation(31), as well as the survival prediction(32). Lu et al. developed a nomogram based on the contrast-enhanced CT, which showed favorable performance in predicting LNM in PTC patients with an AUC of 0.867(33). Nevertheless, iodinated contrast agents have a risk of contrast allergy and might delay the RAI in PTC patients, which limits its clinical application. Hu et al. established an MRI radiomics model which obtained good accuracy in predicting LNM status preoperatively(6). However, MRI is expensive, time-consuming, and not routinely performed for PTC patients in clinical management.

Our previous study has demonstrated the feasibility of applying the US-based radiomics analysis for assessing the risk of LNM in PTC patients(16). Jiang et al. established a nomogram which combined the shear-wave elastography (SWE) radiomics signature and clinicopathological parameters achieved

satisfactory predictive value for LN staging in PTC patients, with an AUC of 0.851 and 0.832 in the training and validation cohort, respectively(23). These US radiomics studies were designed to predict the cervical LNM, however, the treatment strategy for LNM in the central or lateral compartment vary greatly. Thus, accurate radiomics models for predicting LNM in central or lateral compartment, respectively, are urgently needed.

Here, we attempted to develop two US radiomics nomograms for predicting the central and/or lateral LNM preoperatively. We investigated the association between central/ lateral LNM and preoperatively available characteristics by univariate analysis. Age, US-reported central CLN status, and radiomics signature were identified as the independent predictors for central LNM; US-reported lateral CLN status and radiomics signature were identified as the independent risk factors for lateral LNM, respectively, by multivariate logistic regression analyses. Then, two nomograms were developed based on the multivariate analyses. Interestingly, the independent risk factors on which the two nomograms were based in this study were also the independent risk factors for central/lateral LNM in our previous studies(15, 20). This may indicate the great predictive value of these factors for cervical LNM in PTC patients. The nomograms have been confirmed to be capable of generating a probability of central/lateral LNM preoperatively and individually, which is in line with the prevailing concept of personalized precision medicine. The calibration curve showed superior consistency between nomogram-estimated and actual observed probability in each of the cohort. For the clinical usefulness of the nomograms, we employed DCA to evaluate whether the nomogram-assisted decision-making would improve the patient outcomes. Our results demonstrated that the nomogram supplied better clinical net benefit across the majority range of reasonable threshold probabilities than either the radiomics signature or the US-reported CLN status.

Some limitations have to be acknowledged in this study. First, the gene mutation status was not included in this study. Recently, increasing studies have been conducted to investigate the association between gene mutation and the LNM in PTC. Since not all the patients received the BRAF mutation examination after FNA, the role of gene mutation as an independent predictor still needs to be further studied. Second, the radiomics features were only extracted from conventional US images. However, multimodal US technology, such as SWE or contrast-enhanced US, has been applied jointly for the diagnosis of thyroid nodules in clinical practice, a new radiomics study incorporating multimodal technology is ongoing at our center. Third, the utilized images were obtained from the same US system. Radiomics features have been reported to be affected by the US machine and parameters used for image acquisition, thus, a multi-center study with multiple US systems is needed to acquire high-level evidence for further clinical application.

In conclusion, we developed an easy-to-use and noninvasive predictive tool which incorporates the radiomics signature and clinical characteristics to preoperatively evaluate the individual risk of cervical central/lateral LNM in patients with PTC. The nomograms proposed here hold promise for optimizing the personalized treatment, which may improve the survival outcome in PTC patients.

Abbreviation List

LNM	Lymph node metastasis
PTC	Papillary thyroid carcinoma
US	Ultrasound
CLN	Cervical lymph node
LN	Lymph node
CT	Computed tomography
FNA	Fine-needle aspiration
CCND	Central compartment neck dissection
RAI	Radioactive iodine
Rad-score	Radiomics score
AUC	Area under the ROC curve
TSH	Thyroid stimulating hormone
TG	Thyroglobulin
TPOAB	Thyroglobulin antibody
ICC	Interclass correlation coefficient
LASSO	Least absolute shrinkage and selection operator
ROC	Receiver operating characteristic
DCA	Decision curve analysis
SD	Standard deviation
SWE	Shear-wave elastography

Declarations

Ethics approval and consent to participate

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. All data included in the present study was collected after obtaining ethical approval from the institutional review boards at Fudan University Shanghai Cancer Center, Fudan University Shanghai Cancer Center, Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University, and Zhongshan Hospital, Fudan University (No. 1802181-22-NSFC). This retrospective study was approved by the Ethics Committees of all participating hospitals

(Fudan University Shanghai Cancer Center; Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University; Zhongshan Hospital, Fudan University), and performed in accordance with the Declaration of Helsinki. The need for informed consent was waived by the Institutional Review Boards of Fudan University Shanghai Cancer Center, Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University; Zhongshan Hospital, Fudan University, because of the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Performance of the different models in predicting the central LNM in PTC patients. (a) ROC curves of US-reported central LN status, radiomics signature, and radiomics nomogram for predicting central compartment LNM in the training cohort; (b) in the internal validation cohort; and (c-d) in two external validation cohorts. ROC, receiver operation characteristic; US, ultrasound; LN, lymph node; LNM, lymph node metastasis.

Figure 2

Performance of the different models in predicting the lateral LNM in PTC patients. (a) ROC curves of US-reported lateral LN status, radiomics signature, and radiomics nomogram for predicting lateral compartment LNM in the training cohort; (b) in the internal validation cohort; and (c-d) in two external

validation cohorts. ROC, receiver operation characteristic; US, ultrasound; LN, lymph node; LNM, lymph node metastasis.

Figure 3

US-based radiomics nomograms used for prediction of (a) central compartment and (b) lateral compartment LNM in patients with PTC. US, ultrasound; LNM, lymph node metastasis; PTC, papillary thyroid carcinoma.

Figure 4

Calibration curve evaluate the radiomics nomogram used for prediction of central LNM (a) in the training cohort ($p=0.182$), (b) internal cohort (0.427), and (c-d) in two external cohorts ($p=0.561$, $p=0.894$). The Hosmer-Lemeshow tests yield nonsignificant statistics. LNM, lymph node metastasis.

Figure 5

Calibration curve evaluate the radiomics nomogram used for prediction of lateral LNM (a) in the training cohort ($p=0.722$), (b) internal cohort ($p=0.326$), and (c-d) in two external cohorts ($p=0.637$, $p=0.589$). The Hosmer-Lemeshow tests yield nonsignificant statistics. LNM, lymph node metastasis.

Figure 6

Decision curve analysis for each model in predicting (a) central compartment and (b) lateral compartment LNM in PTC patients. The y-axis represents the net benefit, which was calculated by summing the benefits (true positives) and subtracting the harms (false positives), and weighing the relative harm of false-positive and false-negative results. According to threshold probability obtained, the radiomics nomograms have the greatest net benefit compared with other models or simple strategies such as all-treat and non-treat scheme do. LNM, lymph node metastasis; PTC, papillary thyroid carcinoma.