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# Ultrasonography features and American college of radiology thyroid imaging reporting and data system category in the prediction of central lymph node metastasis in papillary thyroid carcinoma

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► ***Original article***

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## ABSTRACT

***Background***: The assessment of central lymph node metastasis before operation guides the surgical plan for patients with papillary thyroid carcinoma (PTC). The aim of this study was to investigate the predictive value of the ultrasonography (US) features and American College of Radiology Thyroid Imaging Reporting and Data System (ACR-TIRADS) category in central lymph node metastasis in papillary thyroid carcinoma patients. ***Materials and Methods:*** The retrospective study of 346 papillary thyroid carcinoma patients who received diagnosis and treatment at the authors' institution from May 2016 to December 2021 was performed. The tumors were categorized based on the US features as well as the Kwak-TIRADS or ACR-TIRADS respectively. Correlation between US features and cervical lymph node metastasis (CLNM), as well as the effects of different TI-RADS categories on the prediction of CLNM were evaluated. ***Results:*** A total of 164 PTC patients (47.4%) were identified with CLNM. In univariable analysis, age (P<0.001), maximum diameter (P<0.001), clinging to the capsule (P<0.001), shape (P=0.003), and ACR-TIRADS score (P<0.001) exhibited significant association with cervical lymph node metastasis in PTC patients. In multivariable analysis, age, maximum diameter, taller-than-wide shape, and clinging to the capsule were the independent factors for CLNM (P<0.05). ACR-TIRADS score was also the independent factor for CLNM (OR=1.230, 95%CI 1.016-1.488, P=0.033). ***Conclusions:*** The study indicated that preoperative ultrasonography features and the ACR-TIRADS category based thereon are effective to evaluate the CLNM risk and of diagnostic value for PTC patients.

## INTRODUCTION

In the past decade, the annual incidence rate of thyroid carcinoma has shown significant increase, which is in part due to the growing detection rate. Among all histological subtypes, papillary thyroid carcinoma (PTC) constitutes the vast majority [1-4]. PTC is characterized by low degree of malignancy, and discussions around overdiagnosis and overtreatment of the disease, especially unnecessary neck lymph node dissection remain controversial.

The incidence rate of cervical lymph node metastasis (CLNM) in papillary thyroid carcinoma can be up to 40–90%. CLNM is the main risk factor for the recurrence of PTC [5]. Generally, the metastasis of lymph nodes first appears in the central compartment and develops to the lateral compartment in PTC, and still possesses the nature of jumping metastasis [6]. Preoperative assessment of the risk of CLNM is suggested for the evaluation of the surgery range, particularly whether the dissection of lymph node is necessary following the guidelines of American thyroid association [7-11]. It is difficult to confirm CLNM preoperatively, and the identification of sensitive risk factors for CLNM is of critical importance to avoid needless surgeries.

TIRADS categories are risk assessment systems based on ultrasonography features, with high sensitivity in the evaluation of the malignancy risk of thyroid nodules [12-14]. The American college of radiology (ACR)-TIRADS with superior diagnostic performance has reduced the unnecessary fine-needle aspiration (FNA), which is possibly associated with its high size threshold for FNA. Whereas, the ACR-TIRADS conducts a rather complex computational to assign scores to each of the US features of the 5 morphological categories under the interpretation and assignment of radiologists [15]. On

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the contrary, the Kwak-TIRADS scores the suspected American characteristics by adding up to form a numerical score with a final category, and is regarded as a simple and practical system. In spite of the criticism on Kwak-TIRADS for giving equal weight to each suspect US feature, recent studies have revealed its higher diagnostic value compared with ACR-TIRADS when FNA is recommended regardless of the size threshold [16].

Kwak-TIRADS and ACR-TIRADS are widely used categories in clinical trials, but few studies have reported the comparison of Kwak-TIRADS and ACR-TIRADS for CLNM prediction in patients with PTC. Our work intended to analyze the ultrasonography (US) features of papillary thyroid carcinoma, and to compare the predictive value of Kwak-TIRADS and ACR-TIRADS in CLNM, which might provide reference for clinical diagnosis and treatment.

## MATERIALS AND METHODS

### *Patients and clinical data*

The Ethics Committee of the Suzhou science and technology town hospital authorized this study (IRB202007001RI), and informed consent was signed by all participants. The clinical information of 403 thyroid carcinoma patients who received diagnosis and treatment at our institution from May 2016 to December 2021 was retrospectively analyzed. Inclusion criteria: (1) postoperative pathology confirmed PTC; (2) patients who underwent neck ultrasonography before surgery. The following patients were excluded: (1) patients who did not undergo neck lymph node dissection (n=55); (2) patients who had the pathological type of thyroid follicular carcinoma (n=2); (3) received no anti-PTC therapy before surgery. When the number of suspicious malignant nodules detected by preoperative US was more than one, only the largest one was selected. Totally 346 patients with 141 males and 205 females were ultimately enrolled in this study (mean age: 38.3±10.6, mean size: 13.7±5.8). They were divided to the group with CLNM (n=164) or without CLNM (n=182) according to the presence or absence of CLNM.

### *Ultrasonography analysis*

Representative images of patients were generated by PHILLIP EPIQ7 scanner (Diagnostic Ultrasound System and Transducers, Philips Ultrasound, Inc, USA) with the equipment of a 9L linear array transducer. All patients were diagnosed by 5 sonographers with 5-12 years of working experience. The images of all patients were retrospectively analyzed, and the US features were recorded, including maximum diameter, tumor location, internal composition, echogenicity, margin, shape, clinging to the capsule, echogenic foci (table 2). Suspicious malignancy features such as hypoechogenicity or significant hypoechogenicity, solid composition, marginal differential lobes or irregularities, microcalcifications, and taller-than-wide shape were evaluated based on US findings.

### *TI-RADS categories*

All nodules were assessed by Kwak-/ACR-TIRADS in accordance with their US features. The classification and ACR-TIRADS score were recorded respectively.

Kwak-TIRADS is based on the quantity of suspicious signs of malignancy (hard texture, hypoechoic, irregular margins, microcalcifications and taller-than-wide). Nodules without any suspicious signs of malignancy were graded 3 (risk 1.7%), and those with 1, 2, 3, 4, and 5 suspicious malignant signs were divided into 4A (risk 3.3%), 4B (risk 9.2%), 4C (risk 44.4-72.4%), and grade 5 (risk 3.3%) [17].

ACR-TIRADS is a scoring system based on five US features (composition, echogenicity, margin, shape and echogenic foci). Each US feature has several types, each of which is assigned a score respectively. The total score is then calculated to access the ACR-TIRADS level, which ranges from TR1 (0 points, benign) to TR5 (greater than or equal to 7 points, highly suspicious for malignancy) [18].

### *Statistical analysis*

Results were analyzed by the SPSS software (IBM Corporation, USA). Count data are presented as percentages. Measurement data are shown as the mean± standard deviation (SD). The comparison of qualitative variables between patients with or without CLNM was subject to Chi-square and Fishers' exact tests. The t test was applied for comparison of quantitative variables between patients in both groups. The risk factors with statistical difference in univariate analyses were subject to logistic regression analyses. The receiver operating characteristic (ROC) curve was applied to evaluate the diagnostic value of the risk factors as well as the model, and then the diagnostic sensitivity and specificity were obtained. *P* value less than 0.05 was set as the threshold value.

## RESULTS

### *Univariate analyses of the associations between clinical characteristics and CLNM in PTC patients*

Patient clinical characteristics were shown in table 1. This analysis included 346 PTC patients, with 164 patients with CLNM (47.4%) and 182 patients without CLNM (52.6%). The average age was 31.09±10.58 in patients with CLNM and 42.37±10.26 in patients without CLNM

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($X^2$=9.911; $p$<0.001). In the CLNM group, male patients accounted for 41.5% and female patients accounted for 58.5%. Among participants without CLNM, male patients occupied 40.1% and female patients accounted for 59.9% ($X^2$=0.065; $p$=0.798). The mean tumor maximum diameters were 11.97±3.15 mm with CLNM, which were significantly higher than those without CLNM (9.04±3.18 mm, $t$=8.843, $P$<0.001).

**Table 1.** Univariate analysis of associations of clinical characteristics with CLNM in PTC patients.

| Clinical features | CLNM | | $X^2/t$ | *P* value |
|---|---|---|---|---|
| | Yes (n=164) | No (n=182) | | |
| Gender | | | 0.065 | 0.798 |
| Male | 68 (41.5%) | 73 (40.1%) | | |
| Female | 96 (58.5%) | 109 (59.9%) | | |
| Average age | 31.09±10.58 | 42.37±10.26 | 9.911 | *<0.001 |
| Mean maximum diameter | 11.97±3.15 | 9.04±3.18 | 8.843 | *<0.001 |

### *Univariate analyses of the associations of PTC patient ultrasonography features with CLNM*

The US features of the patients were summarized in table 2. Among the US features recorded, shape and clinging to the capsule were significantly correlated with CLNM ($X^2$=8.621, $P$=0.003; $X^2$=71.591, $P$<0.001, respectively). However, location ($X^2$=1.718, $P$=0.190), margin ($X^2$=6.299, $P$=0.098) internal composition ($X^2$=1.164, $P$=0.559), echogenicity ($X^2$=3.288, $P$=0.349), echogenic foci ($X^2$=6.264, $P$=0.099), and internal blood flow ($X^2$=1.309, $P$=0.308) were not associated with CLNM statistically.

### *Univariate analysis of the associations between Kwak-TIRAS and ACR-TIRADS category in PTC patients*

All nodules were evaluated by Kwak-TIRADS category and ACR-TIRADS category respectively (table 3). ACR-TIRADS category was revealed to be significantly correlated with CLNM ($X^2$=62.849, $P$=0.000). The proportion of Kwak-TIRADS grade-5 nodules in the group with CLNM (62%, 37.8%) was remarkably lower than that in the group without CLNM (78%, 42.8%). The total score of each tumor was then calculated according to the ACR-TIRADS category. The ACR-TIRADS scores of the CLNM group were significantly higher than those in the group without CLNM ($t$=11.440, $P$<0.001), while no significant association was found between Kwak-TIRADS category and CLNM ($t$=5.138, $P$=0.162).

### *Multivariate analysis of PTC patients*

According to the univariate analysis, statistically significant factors were selected and subject to the multivariate analysis (table 4). Age ($P$=0.020), size ($P$=0.034), shape ($P$=0.000), and clinging to the capsule ($P$=0.002) were the independent factors of CLNM. ACR-TIRADS score was also an independent factor of CLNM ($P$=0.033).

**Table 2.** Univariate analyses of associations between PTC patient ultrasonography features and CLNM.

| Ultrasonography features | CLNM | | $X^2$/ *Fisher* | *P* value |
|---|---|---|---|---|
| | Yes (n=164) | No (n=182) | | |
| Margin | | | 6.299 | 0.098 |
| smooth | 6(3.7%) | 7(3.8%) | | |
| Ill-defined | 59(36.0%) | 83(45.6%) | | |
| Lobulated/irregular | 96(58.5%) | 92(50.5%) | | |
| Extra-thyroidal extension | 3(1.8%) | 0(0%) | | |
| echogenicity | | | 3.288 | 0.349 |
| anechoic | 9(5.5%) | 6(3.3%) | | |
| Hyperechoic/ isoechoic | 48(29.3%) | 62(34.1%) | | |
| hypoechoic | 84(51.2%) | 97(53.3%) | | |
| very hypoechoic | 23(14.0%) | 17(9.3%) | | |
| echogenic foci | | | 6.264 | 0.099 |
| none or large comet-tail artifacts | 42(25.6%) | 31(17.0%) | | |
| macrocalcifications | 12(7.3%) | 24(13.2%) | | |
| peripheral calcifications | 8(4.9%) | 7(3.8%) | | |
| punctate echogenic foci | 102(62.2%) | 120(66.0%) | | |
| shape | | | 8.621 | *0.003 |
| wider than tall | 66(40.2%) | 112(61.5%) | | |
| taller than wide | 98(59.8%) | 70 (38.5%) | | |
| location | | | 1.718 | 0.190 |
| isthmus | 48(29.3%) | 42(23.1%) | | |
| bilateral of the thyroid gland | 116(70.3%) | 140(76.9%) | | |
| clinging to the capsule | | | 71.591 | *<0.001 |
| no | 48(29.3%) | 136(74.7%) | | |
| yes | 116(70.7%) | 46(25.3%) | | |
| internal composition | | | 1.164 | 0.559 |
| cystic or spongiform | 24(14.6%) | 22(12.1%) | | |
| mixed cystic and solid | 36(22.0%) | 48(26.4%) | | |
| solid | 104(63.4%) | 112(61.5%) | | |
| internal blood flow | | | 1.309 | 0.308 |
| yes | 106(64.6%) | 126(69.2%) | | |
| no | 58(35.4%) | 56(30.8%) | | |

**Table 3.** Univariate analysis of CLNM in PTC with Kwak-TIRADS and ACR-TIRADS.

| TI-RADS category | CLNM | | $X^2/t$ | *P* value |
|---|---|---|---|---|
| | Yes (n=164) | No (n=182) | | |
| Kwak-TIRADS | | | 5.138 | 0.162 |
| 4A | 14 (8.5%) | 24 (13.2%) | | |
| 4B | 28 (17.1%) | 32 (17.6%) | | |
| 4C | 60 (36.6%) | 48 (26.4%) | | |
| 5 | 62 (37.8%) | 78 (42.8%) | | |
| Mean ACR-TIRADS score | 8.84±2.12 | 6.92±1.36 | 11.440 | *<0.001 |

**Table 4.** Multivariate analysis of PTC patients.

| | | B | S.E. | Wals | Sig. | Exp(B) | 95% *CI* |
|---|---|---|---|---|---|---|---|
| Age | | -0.047 | 0.020 | 5.379 | 0.020 | 0.954 | 0.916-0.993 |
| Shape | Wider-than-tall | -1.172 | 0.316 | 13.717 | 0.000 | 0.310 | 0.167-0.576 |
| | Taller-than-wide | | | | | | |
| Maximum diameter | | 0.110 | 0.052 | 4.520 | 0.034 | 1.116 | 1.009-1.234 |
| Clinging to the capsule | no | -1.027 | 0.331 | 9.645 | 0.002 | 0.358 | 0.187-0.685 |
| | yes | | | | | | |
| ACR-TIRADS score | | 0.207 | 0.097 | 4.526 | 0.033 | 1.230 | 1.016-1.488 |

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***Diagnostic performance of the ultrasonography features***

The diagnostic performance of the factors with statistical significance in multivariate analysis was analyzed using ROC curve, which exhibited that the value of AUC (area under the curve) of shape, clinging to capsule, size, ACR-TIRADS score and the model were 0.572, 0.758, 0.781, 0.768 and 0.875, respectively. By calculating the Youden index, the diagnostic sensitivities were determined as 68.3%, 76.8%, 86.0%, 64.6% and 87.8%, respectively. The diagnostic specificities were 46.2%, 74.7%, 72.5%, 82.4%, and 81.3%, respectively. Figure 1 and table 5. Figures 2 shows ultrasonography with CLNM.

**Table 5.** The AUC of Ultrasonography factors for CLNM.

| | AUC | Sig | Sensitivity (%) | Specificity (%) | 95% *CI* |
|---|---|---|---|---|---|
| Taller-than-wide shape | 0.572 | 0.020 | 68.3 | 46.2 | 0.512-0.632 |
| Clinging to the capsule | 0.758 | <0.001 | 76.8 | 74.7 | 0.706-0.810 |
| Maximum diameter | 0.781 | <0.001 | 86.0 | 72.5 | 0.730-0.832 |
| ACR-TIRADS score | 0.768 | <0.001 | 64.6 | 82.4 | 0.716-0.820 |
| All | 0.875 | <0.001 | 87.8 | 81.3 | 0.835-0.914 |

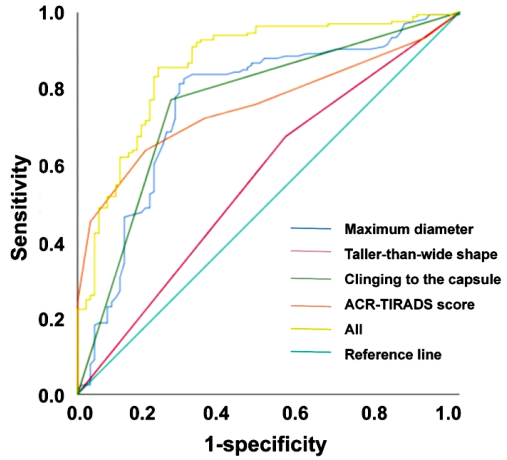



**Figure 1.** The ROC curve for the evaluation of diagnostic performance of the risk factors in papillary thyroid carcinoma patients and the model. ROC, receiver operating characteristics;

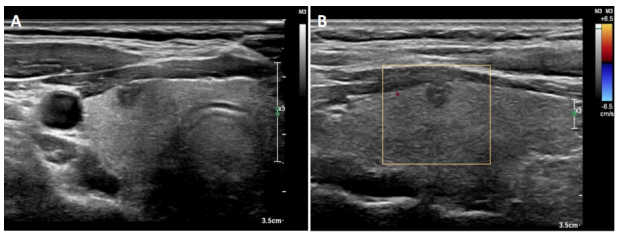



**Figure 2.** Representative ultrasonography findings of papillary thyroid carcinoma patients with CLNM. **(A)** The ultrasonography of the transverse section of PTC patients with CLNM. **(B)** The ultrasonography of the longitudinal section of PTC with CLNM. The tumor was clinging to the capsule, with a maximum diameter of 10 mm and taller-than-wide shape. The ACR-TIRADS category is 5. The ACR-TIRADS score was 12 points. CLNM, cervical lymph node metastasis; ACR-TIRADS, American College of Radiology Thyroid Imaging Reporting and Data System.

## DISCUSSION

With the advancement and widespread use of ultrasound technology, the detection rate of thyroid carcinoma shows steady increase during the past decades. Differentiated thyroid carcinoma accounts for 95% of the total, of which PTC is the most common pathological type [19]. The unnecessary surgery with complications such as hypothyroidism and scarring might have a negative impact on the life quality of patients [20].In recent years, there has been controversy over the overdiagnosis and overtreatment of thyroid carcinoma. However, the presence or absence of central lymph node metastasis still crucially affects the treatment plans and even the surgery decision [21-23]. Ultrasonography and TI-RADS category based thereon play irreplaceable roles in the diagnosis of thyroid carcinoma. Whether ultrasonography and TI-RADS category can predict CLNM in PTC patients has not been explored in literature.

In this study, the rate of CLNM in PTC patients was 48.0%, which was close to what has been reported in the literature (54.1%) [24]. Among the clinical and US features, age, diameter, taller-than-wide shape and clinging to the capsule were independent factors associated with CLNM statistically, which was consistent with the CLNM risk factors reported in the previous literature [25-27]. Age served as a protecting factor for CLNM among PTC patients, indicating that the risk of central lymph node metastasis was inversely proportional to the patient age. High basal metabolic rate, active tumor proliferation and invasive inclination to the adjacent tissues might also be responsible. Diameter greater than 10 mm was also associated with CLNM. The risk of invading and breaking through the capsule increased along with the tumor growth, which might eventually lead to metastasis. PTC progressed slowly in general. With the increase in tumor size and proliferation, the risk of CLNM increased. The taller-than-wide shape reflected expansibility and proliferation of the tumor, which conformed to the characteristics of malignant tumor. The tumor with taller-than-wide shape was more likely to invade and break through the capsule, which led to CLNM eventually. Tumors clinging to the capsule were more likely to break through the capsule and develop into CLNM.

Based on the analysis of the sensitivity and specificity of each statistically associated factor, hypoechoic, diameter more than 10 mm, and higher ACR-TIRADS scores had relatively high diagnostic performance. Central lymph nodes are located between the sternum and hyoid bone, anterior to the trachea and close to the thyroid gland. Their deep location results in a difficulty in the preoperative diagnosis by ultrasound. Chen K [28] has reported that the ACR-TIRADS category is significantly correlated with CLNM in patients with PTC. The higher ACR-

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TIRADS score in CLNM group was identified in comparison with the group without CLNM, which had a better performance in sensitivity and specificity. In this study, we compared the Kwak/ACR-TIRADS, which are two widely used classification systems. The results showed that there was no association between Kwak-TIRADS category and CLNM, while ACR-TIRADS was significantly associated with CLNM, suggesting that the ACR-TIRADS category was also of predictive value for CLNM in PTC patients. Based on the ROC curve of ACR-TIRADS score, we further verified the role of ACR-TIRADS classification in the prediction of CLNM. It is critical to analyze the US features and repeat scanning when necessary to assess the risk of CLNM. As reported in the literature, the proportion of hypothyroidism or subclinical hypothyroidism in PTC patients is about 13% [29]. For such patients, the risk of CLNM should be carefully evaluated preoperatively. Unnecessary surgical resection would further aggravate hypothyroidism, which may impair the life quality of patients. Notably, ACR-TIRADS score was strongly correlated with CLNM in multivariate analysis, while echo, calcification and margin on which ACR-TIRADS score was based were not correlated with CLNM, suggesting that comprehensive analysis was essential for diagnosis and prognosis evaluation.

The study has several limitations. First, there may be some deviation in the selection of samples. Participants without surgery or neck lymph node dissection were excluded in the study. Secondly, subjective factors of the sonographer cannot be completely eliminated during scanning and image analysis. Lastly, a study with large sample size in multiple centers needs to be executed to confirm the result furthermore.

In conclusion, age, maximum diameter, clinging to the capsule and taller-than-wide shape were independent risk factors associated with CLNM in PTC patients. US features based ACR-TIRADS category shows a certain predictive value of CLNM in PTC patients. The diagnostic efficiency is higher when combined with the predictive factors. For tumors with higher ACR-TIRADS scores, the risk of CLNM should be evaluated carefully by ultrasound before surgery, and the scanning should be repeated if necessary. The findings of our work might offer clues for the preoperative diagnosis of CLNM in PTC patients.

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***Ethical consideration*:** This study was approved by the Ethics Committee of the Suzhou science and technology town hospital approved the study (No. IRB2020030).

***Author contribution*:** X.F. and K.Z. were responsible for the study conception and design. W.C., L.Z., J.G. and B.Y. collected the clinical data and conducted the data analysis. The project supervision was done by B.Y.; X.F. and K.Z. wrote the original manuscript and the other authors edited and reviewed the manuscript. All authors read and approved the final version of the manuscript.

***Data availability statement*:** Data included in this article are available from the corresponding authors under reasonable requests.

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