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Clinical diagnostic value of contrast-enhanced ultrasound and TI-RADS classification for benign and malignant thyroid tumors

One comparative cohort study

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Abstract

To evaluate the diagnostic efficacy and clinical value of contrast-enhanced ultrasonography (CEUS) plus TI-RADS classification in benign and malignant thyroid tumors compared with either method alone.

The informed consent was signed all patients. A total of 370 patients with thyroid tumors of TI-RADS category 3 and 4 were recruited, with 432 thyroid nodules. They respectively received routine ultrasonography and CEUS. The nodules were reclassified according to CEUS scoring, and a combined diagnosis was made. The pathological results were taken as the gold standard. The sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and area under the ROC curve were calculated for the 3 diagnostic methods. The diagnostic efficacy was compared by using Student *t* test, Pearson chi-square (χ^2) test, McNemar chi-square (χ^2) test or *Z* test. Student *t* test and logistic regression were employed for comparing different imaging features of benign and malignant thyroid tumors on CEUS and risk analysis.

Of 432 thyroid nodules, there were 258 malignant nodules (59.72%) and 174 benign ones (40.28%). By logistic regression, 6 suspicious features on CEUS were considered significant for differentiating malignant from benign tumors: slow entry of contrast agents during enhancement stage (OR = 15.610, P = .001), slow time to peak (OR = 7.416, P = .002), non-uniform enhancement (OR = 10.076, P = .023), enhancement pattern (irregular) (OR = 36.233, P = .002), enhancement boundary (unclear) (OR = 25.300, P = .012), and no ring-like enhancement (OR = 25.297, P = .004). CEUS plus TI-RADS classification showed a higher diagnostic efficacy for differentiating between benign and malignant thyroid tumors. The Se was 85.66% (0.806–0.896), Sp 83.33% (0.768–0.884), PPV 88.40% (0.836–0.919), NPV 79.67% (0.729–0.851), and AUC 0.867 ± 0.019 (0.815–0.889). The above indicators were of statistical significance as compared with TI-RADS classification or CEUS alone (P < .05).

CEUS can more clearly visualize microvascular distribution of the nodules and offers a new approach to diagnose benign and malignant thyroid tumors. TI-RADS classification plus CEUS is more accurate than TI-RADS classification alone. This combined approach is worthy of clinical popularization.

Abbreviations: ACR = American College of Radiology, CEUS = contrast-enhanced ultrasonography, NPV = negative predictive value, PPV = positive predictive value, PTC = papillary thyroid cancer, Se = sensitivity, Sp = specificity, TI-RADS = Thyroid Imaging Reporting and Data System, US-FNAB = ultrasound-guided fine-needle aspiration biopsy.

Keywords: CEUS, combined diagnosis, thyroid tumor, TI-RADS classification

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This study was approved by the Ethics Committee of Rizhao People's Hospital affiliated Jining Medical University. This study has been performed in accordance with the Declaration of Helsinki. All patients reviewed this Research and written informed consent was obtained from each patient. All authors have approved the submissions.

The authors have no conflicts of interest to disclose.

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1. Introduction

Thyroid nodules are usually caused by thyroid hyperplasia and lesions with abnormal local hardness and structures within the thyroid.[1] Thyroid nodules are the most common neoplasm in the neck region and also one of the most common endocrine system diseases. The incidence of thyroid nodules diagnosed by palpation is about 4% to 7%,[2] and that by ultrasonography varies between 20% and 76%.[3–5] According to autopsy, the incidence of thyroid nodules is 50% to 65%,[6,7] and the malignant transformation rate of thyroid nodules is 5% to 15%.[8,9] According to the latest statistics, the incidence of thyroid cancer in Chinese women was 16.32 per 100,000 in 2013, ranking the fifth of all malignancies.[10] By 2019, 1 study predicts that papillary thyroid cancer (PTC) will become the third most common cancer in women at a cost of $19 to 21 billion in the United States.[11]

How to accurately differentiate benign and malignant thyroid tumors before surgery remains a big challenge.[12,13] An early identification of benign or malignant nature of thyroid nodules can reduce missed diagnosis and delayed treatment, avoiding overtreatment for benign thyroid tumors, thus relieving the physical and psychological pain for the patients and improving patients' life quality.[14] Features of ultrasound include: on-invasiveness, convenience, and high repeatability and can be used to rapidly acquire the radiographic features within the thyroid lesions. Ultrasonography has become the preferred imaging method for preoperative diagnosis, postoperative follow-up, and screening of thyroid nodules.[14,15] To standardize the diagnostic and classification standards for thyroid nodules and to preclude the subjective factors in result interpretation, Horvath et al first published the Thyroid Imaging Reporting and Data System (TI-RADS) by reference to Breast Imaging Reporting and Data System (BI-RADS).[16] Later Park,[17] Kwak,[18] and Russ[19] made revision of the TI-RADS classification. In 2015, American College of Radiology (ACR) released the protocol for ultrasonographic reporting of thyroid nodules.[20] After that, the TI-RADS classification has been widely used in the risk prediction of benign and malignant thyroid nodules.

However, the features of atypical benign and malignant thyroid nodules may overlap on routine ultrasonography, especially for those of TI-RADS category 3 and 4.[21,22] Like other malignant tumors, thyroid neovascularization plays an important part in the growth and metabolism of malignant thyroid tumors.[23,24] Contrast-enhanced ultrasonography (CEUS) provides a non-invasive, real-time, dynamic and continuous observation of microvascular perfusion and hemodynamics in the thyroid lesions. CEUS is suitable to evaluate microvascular changes in thyroid nodules[25,26] and has a bright clinical prospect in differentiating between benign and malignant thyroid nodules.[27,28] The improved TI-RADS, when combined with CEUS, could significantly improve the diagnostic accuracy for thyroid nodules, especially for TI-RADS class-4 thyroid nodules.[29]

TI-RADS classification was combined with CEUS to evaluate thyroid nodules in this study. The value of CEUS in correcting the diagnosis of TI-RADS category 3 and 4 thyroid lesions and differential diagnosis was determined. We attempted to verify that CEUS can make up for the defects of routine ultrasonography in the diagnosis of thyroid nodules, thereby increasing the accuracy of diagnosing benign and malignant thyroid tumors.

2. Materials and methods

2.1. Subjects

The protocol was approved by the ethics committee of Rizhao People's Hospital affiliated Jining Medical University. All patients were informed of the objective and significance of the research and signed the informed consent. From January 2016 to January 2018 a total of 370 cases with 432 thyroid nodules were recruited at Rizhao People's Hospital affiliated Jining Medical University. The inclusion criteria were as follows: thyroid nodules of TI-RADS category 3 and 4 by routine ultrasonography; having received no clinical intervention before ultrasonography; consenting to CEUS. The following conditions were excluded: not willing to receive CEUS; allergic to the contrast agent; women during pregnancy or lactation. Of 370 cases, there were 68 males and 302 females, who were aged 21 to 74 years old with an average of 43.2 ± 11.7 years. Of 432 nodules, 137 nodules (43.29%) were located in the left lateral lobe, 168 (50.46%) in the right lateral lobe, and 27 (6.25%) in the isthmus. The largest diameter was 0.5 to 6.5 cm, with the average of 1.65 ± 1.03 cm. Of 432 thyroid nodules, 398 nodules were pathologically confirmed after surgery; 34 nodules were pathologically examined by ultrasound-guided fine-needle aspiration biopsy (US-FNAB). The pathological results were taken as the gold standard.

2.2. Examination methods

Philips IU22 Colour Doppler Ultrasound System (Holland) was used with L12–5 linear array transducer (frequency, 5.0–12.0 MHz). For CEUS, L9–3 linear array transducer was used (frequency 3.0–9.0 MHz). SonoVue (Bracco, Italy) was the contrast agent and 5 mL of normal saline was added to the dry powder before use. Milky microbubble suspension was prepared by repeated oscillations.

The patients took a supine position with the head tilted back to fully expose the neck. First, routine ultrasonography was performed. The thyroid was scanned on multiple longitudinal and transverse sections. The images were stored, and the size, morphology, boundary, echoic pattern and aspect ratio of the nodules were observed. Microcalcifications were checked within the nodules and any abnormal lymph nodes in the cervical region were also observed. The optimal section of the nodules was chosen for the shift to CEUS in a dual-frame contrast-enhanced mode. The venous access was established in the antecubital fossa and 1.6 mL of microbubble suspension was taken and rapidly injected. After that, the tube was flushed with 5 mL of normal saline. In the meantime, the timer was started and the whole process of CEUS was recorded dynamically (lasting for at least 2 min). During CEUS, the patients were told to keep the patient's posture and calm breathing.

2.3. Image analysis and diagnostic criteria

The images were reviewed blindly by 2 physicians with the title of associate consultant or above who had experience in ultrasonographic diagnosis of thyroid diseases for over 10 years. They were blinded to the clinical symptoms, pathological results or other imaging results of the patients. Any divergence of opinions was settled by discussion and negotiation.

TI-RADS classification was performed according to ACR's protocol.[20] The contents of evaluation included: components and size of nodules, echoes within nodules, aspect ratio, boundary, calcifications, blood supply, and cervical lymph nodes. TI-RADS classification criteria in the present study are shown in Table 1. Nodules of TI-RADS category 3 and 4a were considered benign, and those of TI-RADS category 4b and 4c were considered malignant.

Diagnosis based on CEUS was done according to the literature.[25,26,30] Signs of malignant nodules in CEUS included

Table 1

TI-RADS classification criteria in the present study.

TI-RADS classification	Definition	Risk of malignancy
TI-RADS score 1	normal thyroid	0
TI-RADS score 2	no malignant sign, benign lesions	0
TI-RADS score 3	no malignant sign, high probability of benignity	<5%
TI-RADS score 4a	one malignant sign; possible benignity	5%–10%
TI-RADS score 4b	2 malignant signs; possible malignancy	10%–50%
TI-RADS score 4c	3 or 4 malignant signs; high possibility of malignancy	50%–85%
TI-RADS score 5	5 malignant signs, highly indicative of malignancy	>85%

TI-RADS = Thyroid Imaging Reporting and Data System.

the followings: non-uniform enhancement; low enhancement; concentric enhancement; disconnection or fragmentation of the enhanced envelope. Signs of benign nodules included: uniform enhancement; equal or high enhancement; ring-like enhancement; clear boundary after enhancement with regular morphology; integrity of the enhanced envelope. One point was added for each malignant sign, and 1 point was subtracted for each benign sign. The nodule scoring <1 point was considered benign, and that scoring ≥ 1 point was considered malignant.

Diagnostic criteria for CEUS combined with TI-RADS classification were as follows: TI-RADS category was the same for nodules scoring 0 point by CEUS; the TI-RADS category was lowered for the nodules scoring below zero by CEUS (for example, if the nodule of TI-RADS category 4a scored -1 point by CEUS, then it was lowered to TI-RADS category 3); the TI-RADS category was elevated for the nodules scoring above zero (for example, if the nodule of TI-RADS category 4a scored +1 point by CEUS, then it was elevated to TI-RADS category 4b). The flow chart for the study was shown in Figure 1.

2.4. Statistical analysis

SPSS 20.0 software was used for statistical analysis. Counts were expressed as means (percentages) and compared using chi-square test or Fisher exact test. Measurements were represented as mean $\pm$ standard deviation and compared using 2 independent samples t test. Pathological results by surgical resection or US-FNAB were taken as the gold standard. Using the benign or malignant nature of nodules by pathological examination as dependent variable and the nodule features on CEUS as independent variable, a binary logistic regression model (Backward selection method, α=0.05) was built. Then multiple regression analysis was performed using this model. The sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) were calculated for TI-RADS classification alone, CEUS alone, and CEUS plus TI-RADS classification, respectively. The diagnostic efficacy of the 3 methods was compared using McNemar's chi-square test, and ROC curve was plotted for each method. Confidence intervals for area under the ROC curve (Az) values were estimated on the basis of a 95% confidence level. The significance level was set as α=0.05, with $P<.05$ indicating significant difference.

3. Results

3.1. Pathological results

Of 432 nodules, there were 258 malignant nodules (59.72%) and 174 benign (40.28%). Among the malignant nodules, there were 209 PTC lesions (48.38%), 23 follicular thyroid carcinomas (5.32%), 17 medullary carcinomas (3.94%), and 9 undifferentiated carcinomas (2.08%). Among the benign nodules, there were 126 nodular goiters (29.17%), 31 thyroid adenomas (7.18%), 13 Hashimoto's thyroiditis lesions (3.01%), and 4 nodular goiters with bleeding cystic lesions (0.93%). As shown in Table 2.

3.2. TI-RADS classification of nodules

TI-RADS classification was performed according to ACR's protocol and based on the 2D ultrasonographic characteristics of the thyroid nodules. As shown in Table 3 benign nodes were generally of a lower TI-RADS category, which was predominantly TI-RADS category 3 (n=73) and TI-RADS category 4a (n=66). In contrast, malignant nodules were of a higher TI-RADS category, which was predominantly TI-RADS category 4b (n=95), and TI-RADS category 4c (n=118). The difference was significant revealed by χ^2 test ($P<.001$).

3.3. CEUS characteristics of benign and malignant thyroid nodules

As to microcirculation perfusion, entry of the contrast agent was slow while the exit was fast in malignant nodules. In our cases, slow entry of the contrast agent was most common (76.0%); the time to peak was slower as compared with the surrounding normal tissues (63.5%), whereas the exit was faster (67.1%). There was significant difference in microcirculation perfusion characteristics between the benign and malignant nodules ($P<.001$). In CEUS, typical malignant nodules were shown as low enhancement (74.8%), concentric enhancement (79.8%), non-uniform enhancement (88.4%), enlargement of nodules after enhancement (63.2%), irregular morphology of the enhanced nodules (78.3%), and unclear boundaries after enhancement (83.3%). Typical benign nodules were shown as ring-like enhancement (69.5%). CEUS characteristics were significantly different between the benign and malignant nodules ($P<.001$). See Table 4.

By binary logistic regression of the risk factors for malignancy, 6 CEUS features were found significant and included into the regression equation. Variable coefficient, Wald statistic, risk ratio, 95% CI and test parameters are shown in Table 5. It is easy to see that slow entry of the contrast agent during enhancement stage (OR=15.610, P=.001), slow time to peak (OR=7.416, P=.002), non-uniform enhancement (OR=10.076, P=.023), irregular enhancement pattern (OR=36.233, P=.002), unclear boundary after enhancement (OR=25.300, P=.012), and no ring-like enhancement (OR=25.297, P=.004) were of a higher diagnostic value for malignant nodules.

3.4. Diagnostic results of TI-RADS classification plus CEUS for benign and malignant nodules

Pathological results were taken as the gold standard. The diagnostic efficacy was compared among TI-RADS classification, CEUS, and combination of the 2. As shown in Table 6, 35 benign nodules were mistakenly diagnosed as malignant by TI-RADS classification, with the misdiagnosis rate of 20.11%; 45 malignant nodules were not detected by TI-RADS classification, with the missed diagnosis rate of 17.44% and the accuracy of 81.48%. 29 benign nodules were mistakenly diagnosed by CEUS, with the misdiagnosis rate of 16.67%; moreover, 37 malignant nodules were not detected by CEUS, with the missed diagnosis rate of 14.34% and accuracy of 84.72%. 18 benign nodules were mistakenly diagnosed by TI-RADS classification plus CEUS, with the misdiagnosis rate of 10.34%; 24 malignant nodules were not detected by TI-RADS classification plus CEUS, with the missed diagnosis rate of 9.30% and accuracy of 90.28%. The agreement rate of the 3 diagnostic methods with pathological results was compared using McNemar's χ^2 test, with $P>.05$, which indicated no significant difference. All 3 methods showed a high diagnostic value for thyroid nodules.

3.5. Diagnostic efficacy of TI-RADS classification plus CEUS for benign and malignant nodules

Table 7 shows the Se, Sp, accuracy, PPVs, NPV s and 95% CI of the 3 diagnostic methods. The Se, Sp, PPV and NPV of TI-RADS classification plus CEUS were 90.69% (0.863–0.938), 89.66%

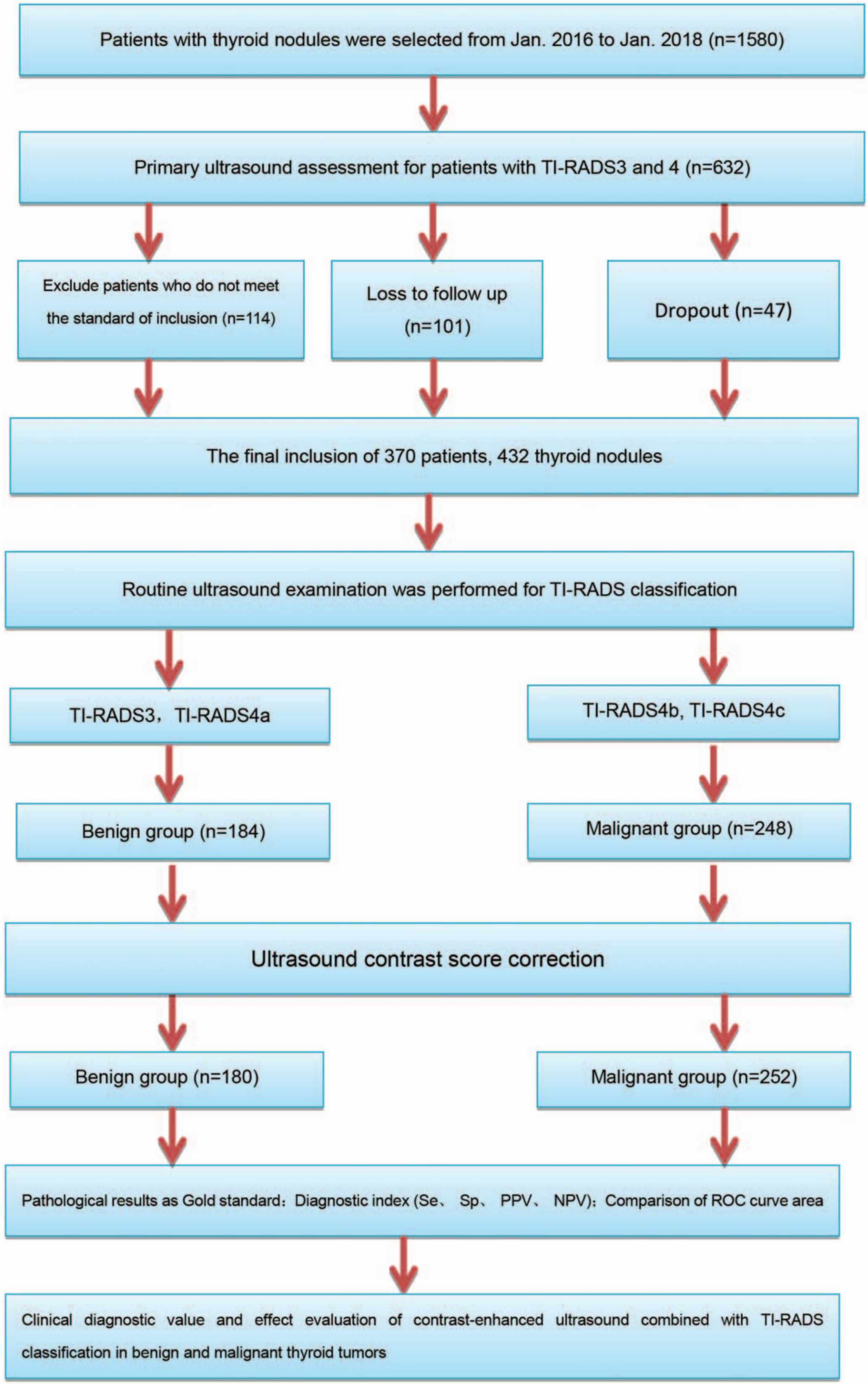

Figure 1. The flow chart for the study.

Table 2

Pathological diagnosis of thyroid nodules (n=432).

Character	Type	Case (n)	Proportion
Malignant	Thyroid papillary carcinoma	209	48.38%
	Follicular thyroid carcinoma	23	5.32%
	Medullary carcinoma	17	3.94%
	Undifferentiated carcinoma	9	2.08%
Benign	Nodular goiter	126	29.17%
	thyroid adenoma	31	7.18%
	Hashimoto's thyroiditis	13	3.01%
	Nodular goiter with hemorrhagic cysts	4	0.93%
Total		432	100%

(0.839–0.936), 92.86% (0.887–0.956), and 86.67% (0.806–0.911), respectively, for benign and malignant thyroid nodules. All these indicators were higher than those using TI-RADS classification or CEUS alone. Significant difference was indicated by the chi-square test (*P* value: .025, .040, .041, .002), and the combined approach thus had a higher diagnostic efficacy.

3.6. ROC curves of TI-RADS classification plus CEUS for benign and malignant nodules

Pathological results were taken as the gold standard. ROC curves were plotted and AUC was calculated for each method. AUC was 0.916 ± 0.015 for TI-RADS classification plus CEUS (95% CI:

Table 3

TI-RADS classification results of benign and malignant thyroid nodules.

Pathology	TI-RADS classification					
Result	Grade 3	Grade 4a	Grade 4b	Grade 4c	χ^2	*P*
Benign	73	66	28	7	178.105	<.001
Malignant	14	31	95	118		

TI-RADS=Thyroid Imaging Reporting and Data System.

Table 4

Contrast-enhanced ultrasound features of benign and malignant thyroid nodules.

Factor	Malignant lesion group (n=258)	Benign lesion group (n=174)	χ^2	*P*
Enhanced phase			285.95*	<.001
Fast entry	9 (3.5%)	130 (74.7%)		
Equal entry	53 (20.5%)	40 (23.0%)		
Slow entry	196 (76.0%)	4 (2.3%)		
the time to peak			128.29*	<.001
Fast	27 (10.5%)	67 (38.5%)		
Equal	67 (26.0%)	90 (51.7%)		
Slow	164 (63.5%)	17 (9.8%)		
Fading phase			152.67*	<.001
rewind down	173 (67.1%)	16 (9.2%)		
Retreating	60 (23.3%)	75 (43.1%)		
slow back	25 (9.6%)	83 (47.7%)		
Enhanced intensity			115.41*	<.001
Low enhancement	193 (74.8%)	53 (28.7%)		
Equal enhancement	41 (15.9%)	30 (17.2%)		
High enhancement	24 (9.3%)	94 (54.1%)		
Enhancement mode			28.65*	<.001
Centrality	206 (79.8%)	100 (57.5%)		
Centrifugal	12 (4.7%)	8 (4.6%)		
Diffusivity	40 (15.5%)	66 (37.9%)		
Enhanced uniformity				
Uniformity	30 (11.6%)	109 (62.6%)	123.93*	<.001
Non-uniform	288 (88.4%)	65 (37.4%)		
Enhanced posterior nodule size			81.96*	<.001
Enlargement	163 (63.2%)	33 (19.0%)		
Unchanged	95 (36.8%)	141 (81.0%)		
Enhanced posterior nodule shape			176.34*	<.001
Regular	56 (21.7%)	151 (86.8%)		
Irregular	202 (78.3%)	23 (13.2%)		
Enhanced posterior nodule boundary				
Clear	43 (16.7%)	139 (79.9%)	170.35*	<.001
Un-clear	215 (83.3%)	35 (20.1%)		
Ring enhancement			205.34*	<.001
Yes	12 (4.7%)	121 (69.5%)		
No	246 (95.3%)	53 (30.5%)		

* The difference between benign lesion group and malignant lesion group was statistically significant (*P*<.05).

Table 5

Logistic regression analysis of risk factors for thyroid malignant nodules.

							95% CI for EXP (B)	
	B	SE	Wald	df	Sig.	Exp (B)	Lower	Upper
Enhanced phase (slow progress)	2.748	0.813	11.434	1	0.001	15.610	3.174	76.762
Peak time phase (slow reaching)	2.004	0.661	9.194	1	0.002	7.416	2.031	27.078
Inhomogeneous enhancement	2.310	1.016	5.168	1	0.023	10.076	1.375	73.848
Enhanced shape (irregular)	3.590	1.182	9.217	1	0.002	36.233	3.569	367.821
Augmented boundary (unclear)	3.231	1.282	6.354	1	0.012	25.300	2.052	311.975
Ring free enhancement	3.231	1.132	8.150	1	0.004	25.297	2.753	232.463
Constant	−15.914	4.481	12.615	1	0.000	0.000		

Table 6

Comparison of TI-RADS classification and contrast-enhanced ultrasound in diagnosis of benign and malignant thyroid nodules (n).

		Pathological results			
Method of examination	Inspection result	Malignant	Benign	McNemar χ^2	*P*
TI-RADS classification	Malignant	213	35	1.013	.314
	Benign	45	139		
Ultrasound contrast	Malignant	221	29	0.742	.388
	Benign	37	145		
Combination	malignant	234	18	0.595	.440
	Benign	24	156		

TI-RADS = Thyroid Imaging Reporting and Data System.

Table 7

Comparison of TI-RADS classification and contrast-enhanced ultrasound in diagnosis of benign and malignant thyroid diseases (%, 95 CI).

Method of examination	Sensitivity	Specificity	Positive predictive value	Negative predictive value
TI-RADS	82.56%(0.772–0.869)	79.89%(0.730–0.854)	85.89%(0.808–0.898)	75.54%(0.686–0.814)
Ultrasound contrast	85.66%(0.806–0.896)	83.33%(0.768–0.884)	88.40%(0.836–0.919)	79.67%(0.729–0.851)
Combination	90.69%(0.863–0.938)	89.66%(0.839–0.936)	92.86%(0.887–0.956)	86.67%(0.806–0.911)
χ^2	7.367	6.453	6.407	12.523
P	.025	.040	.041	.002

TI-RADS = Thyroid Imaging Reporting and Data System.

0.918–0.967, $P<.001$), which was higher than 0.857 ± 0.019 of TI-RADS classification (95% CI:0.820–0.893, $P<.001$) and 0.867 ± 0.019 of CEUS (0.815–0.889). Z test confirmed that there was significant difference ($Z=3.457$, $P=.001$ and $Z=4.005$, $P<.001$, respectively). Our findings suggested that TI-RADS classification plus CEUS had a higher diagnostic value for benign and malignant thyroid nodules (Area > 0.9). See Table 8 and Figure 2.

4. Discussion

TI-RADS classification based on conventional ultrasonography provides a standardization of imaging features of the thyroid, including the number, size, boundary, aspect ratio, internal structure, echoic pattern, and calcification. This is conducive to the communication between radiologists and between radiologists and physicians, while precluding the subjective factors.

Table 8

Comparison of ROC curves between TI-RADS classification and contrast-enhanced ultrasound in thyroid benign and malignant lesions.

				Asymptotic 95% confidence interval	
Test result variable(s)	Area	Std. error[a]	Asymptotic sig.[b]	Lower bound	Upper bound
Combined of 2 methods	0.916	0.015	0.000	0.887	0.946
TI-RADS diagnosis	0.857	0.019	0.000	0.820	0.893
Contrast-enhanced Ultrasound	0.867	0.019	0.000	0.830	0.905

The test result variable(s): Combined of 2 methods, TI-RADS diagnosis, Contrast-enhanced Ultrasound has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

TI-RADS = Thyroid Imaging Reporting and Data System.

[a] Under the nonparametric assumption.

[b] Null hypothesis: true area = 0.5.

[*] Significantly different from the combined of 2 methods ($P<.05$).

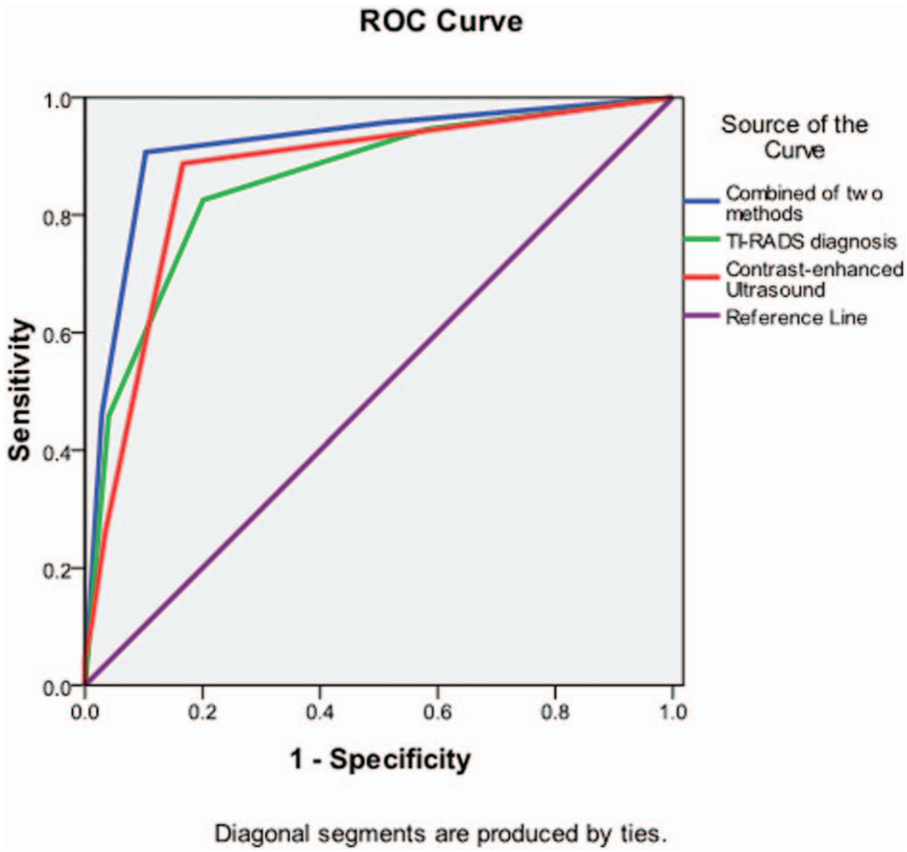

Figure 2. ROC curve of TI-RADS classification plus CEUS for benign and malignant nodules. CEUS = contrast-enhanced ultrasonography, TI-RADS = Thyroid Imaging Reporting and Data System.

TI-RADS classification is an important preoperative diagnostic method using conventional ultrasonography, providing guidance for clinical diagnosis and treatment.[15,31,32] Lin Q et al conducted a regression analysis,[33] which showed that the Se, Sp, PPV, NPV, and accuracy of US-CNB for thyroid nodules of TI-RADS category 4 were 95.7%, 97.8%, 97.8%, 95.7%, and 96.7%, respectively. In our study, the Se of TI-RADS classification for benign and malignant thyroid nodules was 82.56% (0.772–0.869), Sp 79.89% (0.730–0.854), PPV 85.89% (0.808–0.898), and NPV 75.54% (0.686–0.814). These indicators were suggestive of a high diagnostic value.

However, in clinical practice, different ultrasound systems and criteria may be used for TI-RADS classification. The classification criteria are not perfect. For example, some radiologic features of benign and malignant lesions may overlap; the classification of benign and malignant lesions does not cover all types of lesions, and some specific ultrasound features are not included. Moreover, subjective factors cannot be fully excluded. A meta-analysis[34] indicated that the Se (57%–96%) and Sp (43%–93%) of TI-RADS classification may vary greatly. Especially for thyroid nodules of TI-RADS category 3 and 4, which are in a transitional state between benign and malignant, the use of TI-RADS classification is highly controversial and not yet standardized. The nature of the thyroid nodules cannot be determined based on ultrasound features alone,[35] and more diagnostic basis is needed to reduce or prevent misdiagnosis, missed diagnosis, delayed treatment and overtreatment.

CEUS is one of the research hotspots in ultrasound medicine and its application in abdominal viscera[36] is maturing. However, CEUS for superficial organs such as thyroid is still in the exploratory stage. Some literature reports[37,38] have shown that thyroid cancer cells can secrete cytokines that stimulate angiogenesis, thereby increasing the number of vessels within the nodules, causing disordered distribution of vessels and arteriovenous fistula. Therefore, rich disordered blood flow is an important sign supporting the diagnosis. CEUS can make up for the defects of conventional CDFI, by better visualizing the microcirculation of the tissues or lesions.[25,26] In addition, CEUS can also present the intensity of contrast agent perfusion and enhancement in the lesions, entry and exit of the contrast agent,[25,39] as well as more detailed morphological and biological features of vessels in the nodules. Nemec U et al showed that CEUS had a high Sp of 84.8% and a high Se of 76.9%. Our study also confirmed the high diagnostic efficacy of CEUS in benign and malignant thyroid nodules: The Se was 85.66% (0.806–0.896), Sp 83.33% (0.768–0.884), PPV 88.40% (0.836–0.919), NPV 79.67% (0.729–0.851), and AUC 0.867 ± 0.019 (0.815–0.889).

Judging on the enhancement pattern of benign and malignant thyroid nodules on CEUS has always been a difficulty. Previous studies[30,40] have shown that the ultrasound features of a malignant nodule may be as follows: concentric, non-uniform, and low enhancement, with incomplete ring-like enhancement pattern, fast disappearance during the early stage, irregular shape and unclear boundary. In our study, logistic regression model was first used for the diagnosis of benign and malignant thyroid nodules. A total of 6 CEUS features which were statistically significant for the differential diagnosis of benign and malignant thyroid nodules were identified: slow entry of the contrast agent during enhancement stage (OR = 15.610, $P = .001$), slow time to peak (OR = 7.416, $P = .002$), non-uniform enhancement (OR = 10.076, $P = .023$), irregular enhancement pattern (OR = 36.233, $P = .002$), unclear boundary (OR = 25.300, $P = .012$), and no ring-like enhancement (OR = 25.297, $P = .004$).

Based on the TI-RADS classification using conventional ultrasonography, we corrected the results of nodules of TI-RADS category 3 and 4 by using CEUS. The Se of TI-RADS classification plus CEUS was 90.69% (0.863–0.938) for the benign and malignant nodules, Sp 89.66% (0.839–0.936), PPV 92.86% (0.863–0.938), NPV 86.67% (0.806–0.911), and AUC 0.916 ± 0.015 (95% CI:0.918–0.967, $P < .001$). Their indicators were of significant difference as compared with either TI-RADS classification or CEUS alone ($P < .05$).

Generally speaking, CEUS can more clearly visualize microvessel distribution of the lesions and has a certain predictive value for cervical lymph node metastasis.[41] CEUS provides a new approach for differentiating between benign and malignant thyroid nodules. On the basis of TI-RADS classification using conventional ultrasonography, CEUS can be used to correct the risk classification of benign and malignant thyroid nodules. TI-RADS classification plus CEUS proved to be of a high diagnostic value. However, CEUS findings may overlap for atypical benign and malignant thyroid nodules. They are more diversified for thyroid nodules < 1 cm and the diagnostic value is controversial.[42,43] In our study, the misdiagnosis rate of TI-RADS classification plus CEUS was 10.34%, and the missed diagnosis rate was 9.30%. In order to increase the accuracy of TI-RADS classification for thyroid nodules, unified diagnostic criteria for TI-RADS classification and CEUS and clinical trials with higher quality and larger sample size are required. In addition, multi-mode ultrasonography can be used in combination with other new techniques (UE, US-FNAB, US-FNAB with molecular markers, etc.), including CEUS.

4.1. Limitations

1. This study represents a single center's work, so, results have to be confirmed with multi-center studies and a large sample size.
2. Since most of the malignant nodules were papillary carcinomas (48.3%), and a large portion of the benign nodules were nodular goiters (29.17%), this study mainly confirms the diagnostic value of TI-RADS and CEUS for papillary thyroid carcinoma and nodular goiters. The diagnostic value of this method for other benign and malignant thyroid pathological types certainly require further investigations with larger sample size and a multi-center study.

Author contributions

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