Contrast-Enhanced Ultrasound Improves the Accuracy of the ACR TI-RADS in the Diagnosis of Thyroid Nodules Located in the Isthmus

Kontrastverstärkter Ultraschall verbessert die Genauigkeit des ACR-TIRADS bei der Diagnose von Schilddrüsenknoten im Isthmus

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Key words

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ABSTRACT

Objectives To evaluate the diagnostic performance of the American College of Radiology (ACR) Thyroid Image Reporting and Data System (TI-RADS), contrast-enhanced ultrasound (CEUS), and a modified TI-RADS in differentiating benign and malignant nodules located in the isthmus.

Methods This retrospective study was approved by the institutional review board. Informed consent was obtained. Grayscale ultrasound (US) and CEUS images were obtained for 203 isthmic thyroid nodules (46 benign and 157 malignant) in 198 consecutive patients (156 women, mean age: 44.7 years ± 11.3 [standard deviation]; 47 men, mean age: 40.9 years ± 11.0). The area under the receiver operating characteristic curve (AUC) of the diagnostic performance of the ACR TI-RADS, CEUS, and the modified TI-RADS were evaluated.

Results Lobulated or irregular margins (P = 0.001; odds ratio [OR] = 9.250) and punctate echogenic foci (P = 0.007; OR = 4.718) on US and hypoenhancement (P < 0.001; OR = 20.888) on CEUS displayed a significant association with malignancy located in the isthmus. The most valuable method to distinguish benign nodules from malignant nodules was the modified TI-RADS (AUC: 0.863 with modified TR5), which was significantly better than the ACR TI-RADS (AUC: 0.738 with ACR TR5) (P < 0.001) but showed no significant difference with respect to CEUS (AUC: 0.835 with hypoenhancement) (P = 0.205). The diagnostic value was significantly different between CEUS and the ACR TI-RADS (P = 0.028).

Conclusion The modified TI-RADS could significantly improve the accuracy of the diagnosis of thyroid nodules located in the isthmus.

ZUSAMMENFASSUNG

Ziel Bewertung der diagnostischen Leistung des Thyroid Image Reporting and Data Systems (TIRADS) des American College of Radiology (ACR), des kontrastverstärkten Ultraschalls (CEUS) und eines modifizierten TIRADS zur Differenzierung von benignen und malignen Knoten im Isthmus.

Methoden Diese retrospektive Studie wurde durch die Ethikkommission (Institutional Review Board) genehmigt. Die Einverständniserklärungen wurden eingeholt. Graustufen-Ultraschall- (US) und CEUS-Bilder wurden für 203 isthmische Schilddrüsenknoten (46 benigne und 157 maligne) bei 198 konsekutiven Patienten (156 Frauen, Durchschnittsalter: 44,7 Jahre ± 11,3 (Standardabweichung); 47 Männer, Durchschnittsalter: 40,9 Jahre ± 11,0) gewonnen. Die Fläche unter der Receiver Operating Characteristic Curve (AUC) der diagnostischen Leistung von ACR-TIRADS, CEUS und modifiziertem TIRADS wurde bewertet.

Ergebnisse Lobulierte oder unregelmäßige Ränder (p = 0,001; Odds Ratio (OR) = 9,250) und punktförmige echogene Herde (p = 0,007; OR = 4,718) im US und Hypoenhancement (p < 0,001; OR = 20,888) im CEUS zeigten eine signifikante As-

soziation mit Malignität im Isthmus. Die wertvollste Methode zur Unterscheidung von benignen und malignen Knoten war das modifizierte TIRADS (AUC: 0,863 mit modifiziertem TR5), welches signifikant besser war als ACR-TIRADS (AUC: 0,738 mit ACR TR5; p < 0,001), aber keinen signifikanten Unterschied zu CEUS (AUC: 0,835 mit Hypoenhancement) zeigte (p = 0,205). Der diagnostische Wert unterschied sich signifikant zwischen CEUS und ACR-TIRADS (p = 0,028).

Schlussfolgerung Das modifizierte TIRADS konnte die Genauigkeit der Diagnose von Schilddrüsenknoten im Isthmus signifikant verbessern.

Introduction

The thyroid isthmus is a relatively small but central part of the thyroid that links the left and right lobes of the thyroid. Thyroid nodule location has reportedly been an independent risk factor in predicting the risk of malignant nodule [1]. According to previous reports [2–5], malignant nodules located in the thyroid isthmus are more aggressive than those located in the thyroid lobes, including multifocal malignancies, thyroid gland envelope invasion, extrathyroidal extension, and even lymph node metastases. The findings suggest that total thyroidectomy is an appropriate method for malignant nodules located in the isthmus [2, 6]. Among the medical imaging technologies for the examination of the thyroid, grayscale ultrasound (US) is the most commonly used tool, mainly because it provides real-time scanning and simple operation, is cost-effective, and does not use radiation [7]. The American College of Radiology (ACR) Thyroid Imaging Reporting and Data System (TI-RADS) [8] aims to improve the diagnostic accuracy of thyroid nodules by US. Nodules are assigned points based on features in five classifications (composition, echogenicity, shape, margin, and echogenic foci) and are then categorized into one of five TI-RADS risk categories [8]. However, the role of the TI-RADS in the diagnosis of thyroid nodules within the isthmus is still controversial. Hahn et al. [9] reported that malignant thyroid nodules located in the isthmus more frequently presented with a well-defined margin (31.3 %) and a wider-than-tall shape (91.7 %). Though several studies [10–12] have reported that the total accuracy of the ACR TI-RADS in diagnosing thyroid nodules ranged from 52.0 ~ 92.1 %, the accuracies of the ACR TI-RADS in isthmic thyroid nodules were not reported in their studies.

Contrast-enhanced ultrasound (CEUS) is a relatively new technique to display the hemodynamics of thyroid nodules and is considered to be an effective method to distinguish benign from malignant thyroid nodules [13–15]. However, there is no evidence that CEUS can accurately diagnose thyroid nodules located in the isthmus.

The aim of this study was to evaluate the diagnostic performance of the ACR TI-RADS, CEUS, and a modified TI-RADS in distinguishing benign from malignant thyroid nodules located in the isthmus.

Methods

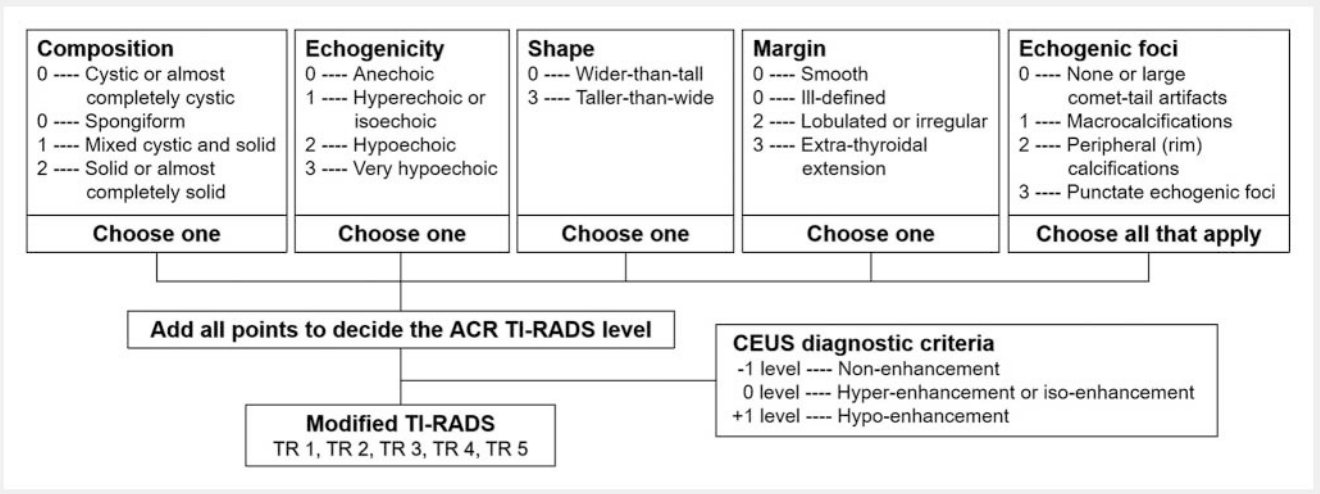
Patients

The local institutional review board approved this retrospective study, and the requirement to obtain informed consent of patients was waived. This study was performed at our institution from January 2015 to December 2018. During this time, the initial population included 227 thyroid nodules located in the isthmus in 222 consecutive patients (age > 18 years). Nodules that were solid, hypoechogenic, lobulated or with irregular margins, taller-than-wide, or contained microcalcifcations on grayscale US were selected for US-guided fine needle aspiration (FNA) [16, 17]. CEUS examination was performed on all thyroid nodules prior to FNA. Pathological diagnosis was based on FNA [18, 19] or surgical results when available. Only benign or malignant nodules were included unless a nodule underwent repeat FNA or surgery that certified benignity or malignancy. Twenty-four nodules were excluded for indeterminate or nondiagnostic pathological results. The final study population comprised 203 nodules from 198 patients (156 women, mean age: 44.7 years ± 11.3 [standard deviation], range: 22 ~ 69 years; 47 men, mean age: 40.9 years ± 11.0, range: 23 ~ 63 years). Of the 198 patients, 5 had two nodules. FNA and surgery were performed on 116 nodules, and 87 had undergone only FNA (active surveillance instead of resection was implemented if nodules were slow-growing, and there was no appearance of lymph node metastases or distant metastases). The median size of the nodules was 0.8 cm (interquartile ranges [IQRs]: 0.6 ~ 1.2).

US and ACR TI-RADS diagnostic criteria

All ultrasonography examinations were performed with two commercially available scanners (Mylab90 [Esaote, Genoa, Italy], equipped with an L523 linear-array transducer for grayscale US and an L522 for CEUS; Resona7 [Mindray, Shenzhen, China], equipped with an L11–3U linear-array transducer for both grayscale US and CEUS). If all or most of the thyroid nodule was located in front of the trachea in a transverse US image, it was defined to be located in the isthmus.

US features were recorded for each thyroid nodule including size (the maximal diameter on US); composition (solid or almost completely solid, mixed cystic and solid, spongiform, and cystic or almost completely cystic); echogenicity (compared to the surrounding normal parenchyma, classified as anechoic, hyperechoic, isoechoic, hypoechoic, or very hypoechoic if the echogenicity was lower than the cervical strap muscle); shape (wider-than-tall or taller-than-wide shape was assessed by measurements, taller-than-wide was defined as the anteroposterior diameter exceeding the transverse diameter in the transverse plane [20]); margin (smooth, ill-defined, lobulated or irregular, and extra-thyroidal extension, extra-thyroidal extension was characterized by loss of the echogenic thyroid capsule or/and frank invasion of perithyroid soft tissue [21]); and echogenic foci (punctate echogenic foci,



▶ **Fig. 1** Flowchart shows the modified TI-RADS classification scheme. If CEUS indicated nonenhancement, one level was subtracted from the ACR TI-RADS category except TR1. If CEUS indicated hypoenhancement, one level was added to the ACR TI-RADS category except TR5. If CEUS indicated hyper- or isoenhancement, the modified TI-RADS category remained the same as the ACR TI-RADS category.

rim or peripheral calcifications, macrocalcifications, and no or large comet-tail artifacts). The nodules were then reclassified following the ACR TI-RADS guideline [8].

CEUS and diagnostic criteria

CEUS was performed with the same instrument used for grayscale US. The contrast medium was SonoVue (BR1; Bracco, Milan, Italy), which is a sulfur-hexafluoride-filled microbubble contrast agent encapsulated by a flexible phospholipid shell. SonoVue was injected intravenously as a bolus at a 1.2 mL dose, followed by 5 mL of normal saline flush. The timer on the ultrasound machine was started, and the imaging plane was kept as stable as possible. Each contrast imaging acquisition lasted at least 2 minutes after the bolus injection and was digitally stored as raw data. If multiple nodules in one patient required CEUS, an interval of 10 minutes was needed to avoid the effects of the last injection.

The CEUS diagnostic criteria are separated into nonenhancement (no enhancing signal visible at the whole nodule), hypoenhancement, isoenhancement, or hyperenhancement compared with the parenchyma of the thyroid gland.

Image interpretation and the modified TI-RADS

Ultrasonography images and videos stored in a computer workstation were reviewed in a random order by two radiologists (with 22 and 17 years of experience in thyroid US) blinded to the patient data. First, each radiologist reviewed the US and CEUS images independently. Subsequently, two radiologists discussed the images in which there was a divergence of their views and reached a consensus on the US features and CEUS enhancement patterns in those cases.

Modified TI-RADS categories were classified on the basis of the following criteria (▶ **Fig. 1**): if the CEUS indicated nonenhancement, one level was subtracted from the ACR TI-RADS category except TR1; if the CEUS indicated hypoenhancement, one level was added to the ACR TI-RADS category except TR5; if CEUS indicated hyper- or isoenhancement, the modified TI-RADS category remained the same as the ACR TI-RADS category.

Statistical analysis

Quantitative data are expressed as the means with standard deviations or medians and IQRs. Groups were compared using the variance, Kruskal-Wallis, chi-squared and Fisher's exact tests depending on distribution. The rankings of valuable features on US and CEUS were evaluated according to the odds ratios (ORs). The weighted kappa statistic (κ) [22] was performed to assess the consistency between the ACR TI-RADS and modified TI-RADS classifications; and interobserver agreement among the two radiologists regarding the ACR TI-RADS classifications, and CEUS enhancement patterns of the nodules. The diagnostic values of the ACR TI-RADS, CEUS and modified TI-RADS were estimated using accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under receiver operating characteristic (ROC) curve analysis, with 95 % confidence intervals (CIs). All statistical analyses were performed with the SPSS, version 16.0 (SPSS, Chicago, IL) and MedCalc Software, version 9.3.8.0 (Mariakerke, Belgium).

Results

Characteristics of patients and isthmic thyroid nodules

Among 203 nodules, 157 were malignant and 46 were benign. Seventeen benign and 99 malignant nodules were certified by histopathological results, while 29 benign and 58 malignant nodules were certified by cytological reports. The detailed pathological types are as follows: the malignant thyroid nodules were all papillary thyroid carcinomas; the benign nodules included 6 inflammatory nodules, 14 adenomatous nodular goiters, 9 hemorrhagic necrotic colloid nodules, 10 nodular goiters, and

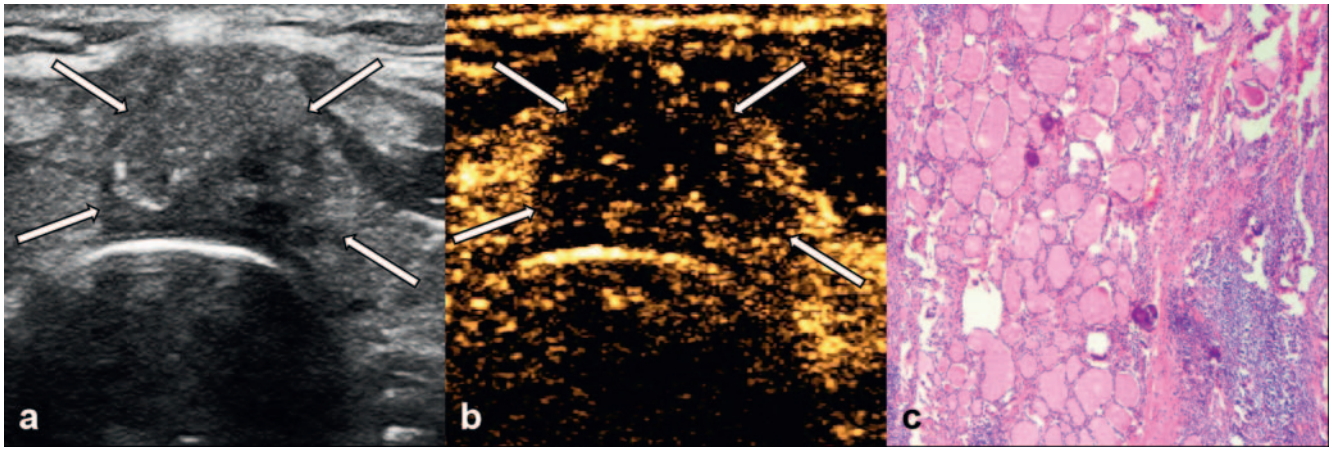
▶ **Table 1** Summary of demographic features and the distributions of US and CEUS features between benign and malignant thyroid nodules located in the isthmus, as well as the values of the significant features

feature	benign nodules	malignant nodules	p-value[#]
no. of nodules	46	157	
no. of patients	45	153	
age, median (IQR), years	51 (37 ~ 56)	42 (34 ~ 52)	0.014[†]
sex			0.065
▪ male	6 (12.0 %)	41 (26.6 %)	
▪ female	40 (88.0 %)	116 (73.4 %)	
nodule size, median (IQR), cm	0.8 (0.5 ~ 1.3)	0.8 (0.7 ~ 1.1)	0.204
composition on US			0.002[†]
▪ cystic or almost completely cystic	0	0	
▪ spongiform	0	0	
▪ mixed cystic and solid	5	1	
▪ solid or almost completely solid	41	156	
echogenicity on US			0.571
▪ anechoic	0	0	
▪ hyper-/isoechoic	2	6	
▪ hypoechoic	43	140	
▪ very hypoechoic	1	11	
shape on US			0.054
▪ wider-than-tall	40	115	
▪ taller-than-wide	6	42	
margin on US			< 0.001[†]
▪ smooth	24	42	
▪ ill-defined	18	43	
▪ lobulated or irregular	4	70	
▪ extra-thyroidal extension	0	2	
echogenic foci[*] on US			< 0.001[†]
▪ none or large comet-tail artifacts	35	76	
▪ macrocalcifications	2	10	
▪ peripheral calcifications	2	0	
▪ punctate echogenic foci	7	75	
CEUS enhancement mode			< 0.001[†]
▪ hypoenhancement	10	134	
▪ isoenhancement	24	22	
▪ hyperenhancement	2	1	
▪ nonenhancement	10	0	

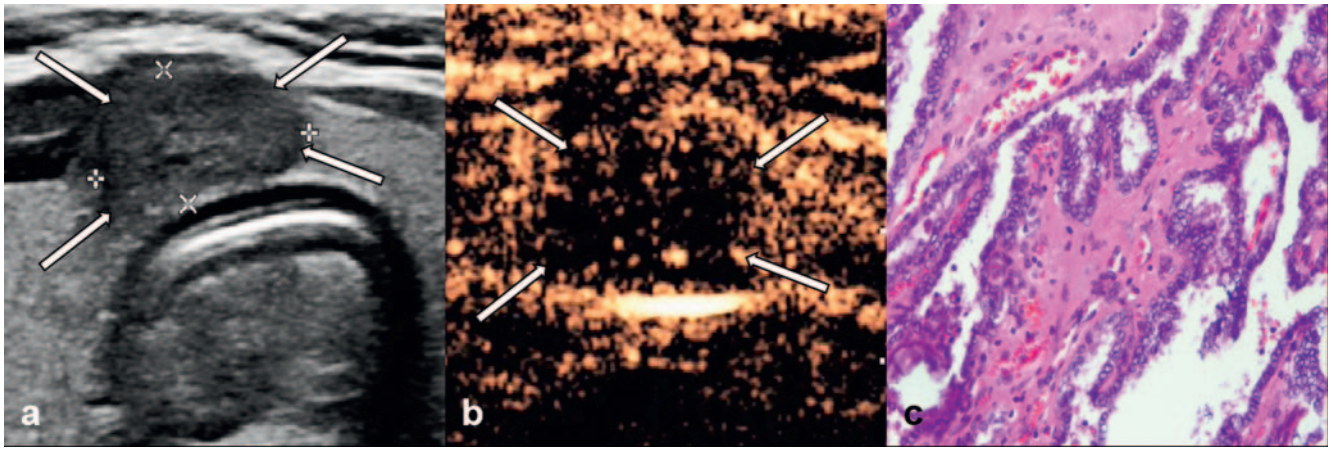
IQR = interquartile range.
[#] A P-value < 0.05 was regarded as statistically significant.
[†] Statistically significant.
[*] Nodules could have more than one type of echogenic foci.

there were 7 nodules coexisting with Hashimoto's thyroiditis in 10 nodular goiters.

The basic features of patients and nodules are outlined in ▶ **Table 1**. Sex (P = 0.065) and nodule size (P = 0.204) were not associated with malignancy. There were significant differences in



▶ **Fig. 2** Images of a 39-year-old woman. **a** A grayscale ultrasound image shows a solid hypoechoic nodule (arrows) located in the isthmus of the thyroid, with ill-defined margins, mixed punctate echogenic foci and macrocalcifications, classified as TI-RADS TR5. **b** A contrast-enhanced image indicated that the nodule was hypoenhanced (arrows). The modified TI-RADS category remained TR5. **c** Pathological image of the lesion, which was a thyroid papillary carcinoma.



▶ **Fig. 3** Images of a 27-year-old woman. **a** A grayscale ultrasound image. A solid hypoechoic nodule (arrows) with smooth margins in the isthmus of the thyroid was classified as TI-RADS TR4. **b** A contrast-enhanced image indicated that the nodule was hypoenhanced (arrows) and classified as modified TI-RADS TR5. **c** Pathological image of the lesion, which was a thyroid papillary carcinoma.

the median age at the time of diagnosis in all patients with malignant (42 years, IQR: 34 ~ 52) and benign (51 years, IQR: 37 ~ 56) nodules (P = 0.014).

Valuable features of US

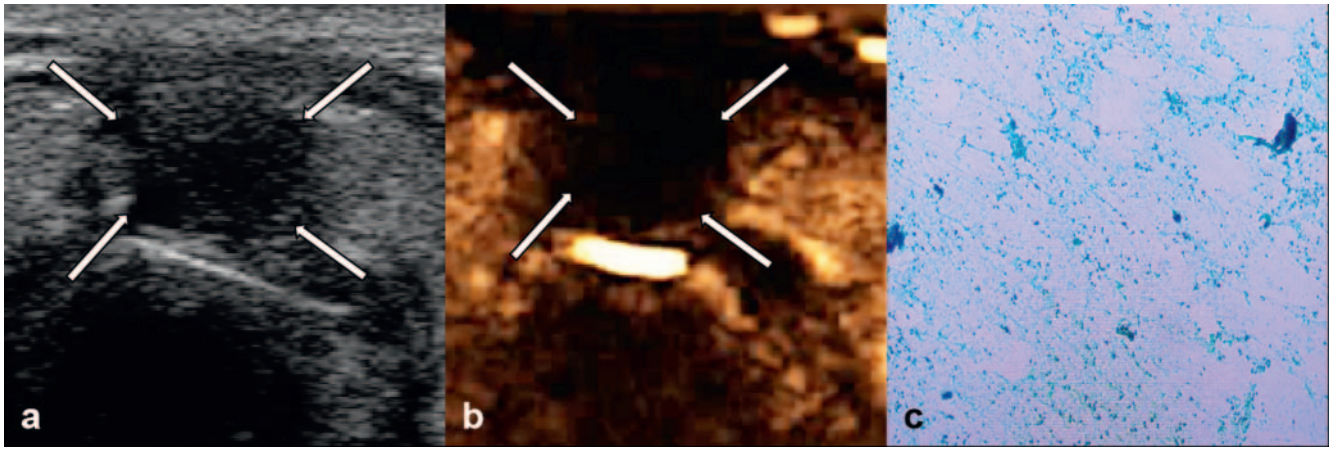
Malignancy located in the thyroid isthmus more frequently had a solid composition (99.0 %), hypoechogenicity (89.2 %), a wider-than-tall shape (73.2 %), punctate echogenic foci (47.8 %), and lobulated or irregular margins (44.6 %) (▶ **Table 1**). Solid or almost completely solid component (P = 0.002), lobulated or irregular margins (P < 0.001) and punctate echogenic foci (P < 0.001) were found more frequently in malignancies, whereas other US features had no value (P > 0.05).

Valuable features of CEUS

Among the 157 malignant nodules, 134 indicated hypoenhancement (▶ **Fig. 2, 3**), 22 indicated isoenhancement, 1 indicated hyperenhancement. Among the 46 benign nodules, 10 indicated hypoenhancement, 24 indicated isoenhancement, 2 indicated hyperenhancement, and 10 indicated nonenhancement (▶ **Fig. 4**). The CEUS diagnostic criteria were associated with malignant nodules (P < 0.001) (▶ **Table 1**).

Rankings of the valuable features of US and CEUS

Three features on US and CEUS displayed a significant association with malignancy located in the isthmus (▶ **Table 2**): lobulated or irregular margins (P = 0.001) and punctate echogenic foci (P = 0.007) on US and hypoenhancement (P < 0.001) on CEUS. The OR of hypoenhancement was 20.888, higher than that of lobulated or irregular margin (OR = 9.250) and punctate echogenic foci (OR = 4.718).



▶ **Fig. 4** Images of a 55-year-old woman. **a** A grayscale ultrasound image. A solid very hypoechoic nodule (arrows) with irregular margins located in the isthmus of the thyroid was classified as TI-RADS TR5. **b** A contrast-enhanced image indicated that the nodule was nonenhanced (arrows). The modified TI-RADS category was TR4. **c** The pathological result was a hemorrhagic necrotic colloid nodule.

▶ **Table 2** Ranks of the most valuable features and their odds ratios.

no.	features of US and CEUS	partial regression coefficient	standard error	p-value	odds ratio	95 % CI
1	punctate echogenic foci on US	1.551	0.576	0.007	4.718	1.526 ~ 14.591
2	solid or almost completely solid component on US	1.704	1.249	0.173	5.496	0.475 ~ 63.588
3	lobulated or irregular margin on US	2.225	0.644	0.001	9.250	2.617 ~ 32.700
4	hypoenhancement on CEUS	3.039	0.485	< 0.001	20.888	8.070 ~ 54.064

Diagnostic accuracies of isthmic thyroid nodules by the ACR TI-RADS, CEUS and the modified TI-RADS

The incidence of malignancy of ACR TI-RADS TR4 and TR5 was 61.3 % and 90.8 %, respectively. The incidence of malignancy of modified TI-RADS TR4 and TR5 was 21.2 % and 93.2 %, respectively, and the incidence of malignancy of isthmic thyroid nodules classified as modified TR4 was dropped from 61.3 % to 21.2 % compared with that of the initial ACR TI-RADS classification (▶ **Table 3**).

In the comparison between ACR TI-RADS and modified TI-RADS classifications (▶ **Table 4**), among the 119 thyroid nodules classified as TR5 by the ACR TI-RADS, 4 were downgraded to TR4 by the modified TI-RADS. Among the 80 thyroid nodules classified as TR4 by the ACR TI-RADS, 46 were upgraded to TR5 and 6 was downgraded to TR3 by the modified TI-RADS. Among the 4 thyroid nodules classified as TR3 by the ACR TI-RADS, 1 was upgraded to TR4 and 1 was downgraded to TR2 by the modified TI-RADS. Among 203 nodules, 145 were categorized in the same risk categories by the ACR TI-RADS and modified TI-RADS classification systems. The consistency between the two classifications was 0.536 (95 % CI 0.419 ~ 0.652).

The AUC of the ACR TI-RADS was 0.738 (95 % CI 0.672 ~ 0.797, P < 0.001) and the best cut-off value for predicting malignancies was > TR4. Application of this cut-off value resulted in a sensitivity of 68.8 % (95 % CI 60.9 ~ 75.9), a specificity of 76.1 % (95 % CI 61.2 ~ 87.4), and an accuracy of 70.4 %. The AUC of modified TI-RADS was 0.863 (95 % CI 0.807 ~ 0.907, $P < 0.001$) and the best cut-off value for predicting malignancies was > TR4. Application of this cut-off value resulted in a sensitivity of 95.5 % (95 % CI 91.0 ~ 98.2), a specificity of 76.1 % (95 % CI 61.2 ~ 87.4), and an accuracy of 91.1 %. The AUC of CEUS was 0.835 (95 % CI 0.777 ~ 0.884, P < 0.001) with hypoenhancement. Application of this cut-off value resulted in a sensitivity of 85.4 % (95 % CI 78.8 ~ 90.5), a specificity of 78.3 % (95 % CI 63.6 ~ 89.1), and an accuracy of 83.7 % (▶ **Fig. 5**). The most valuable method for distinguishing benign nodules from malignant nodules located in the isthmus was the modified TI-RADS, which was higher than the ACR TI-RADS alone ($P < 0.001$) but showed no significant difference with respect to CEUS ($P = 0.205$). The diagnostic value was significantly different between CEUS and the ACR TI-RADS ($P = 0.028$).

Interobserver agreement

The two radiologists showed excellent agreement, with a κ of 0.862 ± 0.036 for the ACR TI-RADS classification and a κ of 0.836 ± 0.039 for CEUS enhancement pattern assessment.

▶ **Table 3** The ACR TI-RADS and modified TI-RADS diagnostic information.

	number of nodules	pathological results/number		malignancy rate (%)
		benign	malignant	
ACR TI-RADS				
▪ TR1	0	0	0	0
▪ TR2	0	0	0	0
▪ TR3	4	4	0	0
▪ TR4	80	31	49	61.3
▪ TR5	119	11	108	90.8
modified TI-RADS				
▪ TR1	0	0	0	0
▪ TR2	1	1	0	0
▪ TR3	8	8	0	0
▪ TR4	33	26	7	21.2
▪ TR5	161	11	150	93.2

▶ **Table 4** Comparison between the ACR TI-RADS and modified TI-RADS classifications.

ACR TI-RADS	modified TI-RADS					total
	TR1	TR2	TR3	TR4	TR5	
TR1	0	0	0	0	0	0
TR2	0	0	0	0	0	0
TR3	0	1	**2**	1	0	4
TR4	0	0	6	**28**	46	80
TR5	0	0	0	4	**115**	119
total	0	1	8	33	161	203

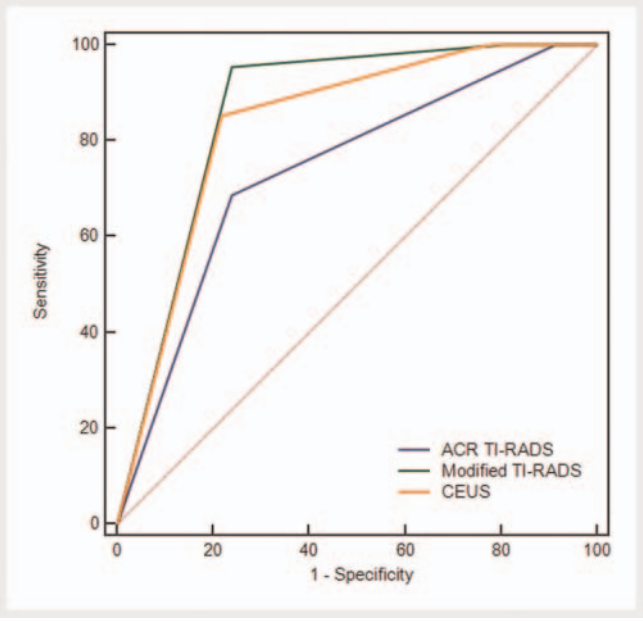
Discussion

Malignant isthmic thyroid nodules are more likely to invade surrounding tissues compared to malignancies located in thyroid lobes [2–5]. Early and correct diagnosis of malignant thyroid nodules located in the isthmus has great significance for clinical treatment selection and outcome prediction.

For 5- to 10-mm suspicious thyroid nodules, when patients have clinical symptoms, suspicious clinical signs, suspicious cervical lymph node metastasis, medical radiation, or contact history of radiotherapy, family history of thyroid cancer, and other high suspicion of thyroid cancer, the standard of FNA should be relaxed appropriately [8]. Thyroid US is gradually included in the routine physical examination in our country, resulting in an increased incidence rate of thyroid nodules suspicious for PTC. Patients are likely to experience fear or anxiety at the thought of leaving their cancer untreated. Therefore, some papillary thyroid microcarcinomas were included in this study.

In the present study, malignancies located in the thyroid isthmus more frequently had a solid composition (99.0 %), hypoechogenicity (89.2 %), a wider-than-tall shape (73.2 %), punctate echogenic foci (47.8 %), and lobulated or irregular margins (44.6 %). The cut-off value for the prediction of malignancies was ACR TI-RADS TR5, and the AUC of the ACR TI-RADS for predicting a malignant nodule was 0.738 in our study, which was lower than previous studies based on malignant thyroid nodules located in the lobe [23, 24]. These variable US features seem to be due to thyroid nodules growing in the narrow isthmic space, which affects the diagnostic result. Improvements can be made in the application of the ACR TI-RADS for the differentiation of benign and malignant thyroid nodules located in the isthmus.

In recent years, CEUS has been introduced to improve the diagnostic performance of grayscale US in thyroid nodules, and the sensitivity and specificity were reported to be 85 % and 82 %, respectively [14]. There is no unified standard and feature of CEUS for the diagnosis of malignancy. Studies from numerous researchers suggest that most of the contrast indicating hypoen-



▶ **Fig. 5** ROC analyses of the diagnostic performance of the ACR TI-RADS, CEUS, and the modified TI-RADS for predicting the malignancy of thyroid nodules located in the isthmus. The AUCs of the ACR TI-RADS, CEUS, and the modified TI-RADS were 0.738, 0.835, and 0.863, respectively.

hancement is malignant thyroid nodules (attributed to the lack of blood supply), whereas most contrast modes indicating high enhancement and circular enhancement are benign nodules [25, 26]. The sensitivity of CEUS in this study is consistent with the results of the aforementioned study [14], and malignancies located in the thyroid isthmus more frequently had hypoenhancement (85.4 %), which indicates that CEUS has similar clinical value in the differential diagnosis of nodules located in the isthmus. However, the specificity (78.3 %) of CEUS was relatively low. Artifacts in CEUS can cause problems regarding diagnosis. A "pseudoenhancement" artifact might occur in thyroid nodules with punctate echogenic foci (microcalcifications) on CEUS examination; it is produced by the nonlinear propagation of the US beam through contrast agent, so that punctate echogenic foci might be mistaken for microbubbles [27, 28].

A previous study found that the ACR TI-RADS combined with CEUS was more accurate than TI-RADS alone [29], but this study included only 6.25 % thyroid nodules located in the isthmus. Thus, the ultimate aim of this study was to assess the diagnostic performance of a modified TI-RADS in thyroid isthmic nodules. The cut-off value of the modified TI-RADS for predicting malignancies was TR5 as well. Nevertheless, the κ value was 0.536 for the agreement of the ACR TI-RADS and modified TI-RADS, which indicated moderate agreement. In our study, a significant difference was observed when the modified TI-RADS was compared with the ACR TI-RADS ($P < 0.001$), indicating that the modified TI-RADS can significantly raise the diagnostic accuracy of isthmic thyroid nodules. The results are consistent with a previous study [29].

There were several limitations in this study. Firstly, 87 nodules were certified by cytological reports. False-negative and false-positive cytological results may have existed. Secondly, all 157 malignancies located in the isthmus were papillary thyroid carcinomas. There were no cases of follicular neoplasms. Studies to analyze the TI-RADS and CEUS in follicular neoplasms located in the isthmus are anticipated. Thirdly, because it was hard to select two ROIs (a single ROI contained the whole nodule, and a similar ROI area was selected from adjacent normal thyroid tissue as a reference) within the narrow isthmic space in transverse sonogram, we did not perform a quantitative CEUS evaluation. Although a meta-analysis of seven eligible studies concluded that the qualitative CEUS evaluation showed better sensitivity and specificity in the diagnosis of thyroid nodules compared with the quantitative CEUS evaluation [15], the quantitative analysis of CEUS in the diagnosis of thyroid isthmic nodules in this study had not been performed, which needs to be evaluated in the future. Finally, this study represents the work of a single thyroid clinic, there is always the risk of potential bias with respect to data collection, and the number of cases was relatively small. These results should be confirmed by a large sample size in a multi-center study.

In conclusion, the present study suggested that the modified TI-RADS could significantly increase the diagnosis accuracy of thyroid nodules located in the isthmus.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Jasim S, Baranski TJ, Teefey SA et al. Investigating the Effect of Thyroid Nodule Location on the Risk of Thyroid Cancer. Thyroid 2020; 30: 401–407

[2] Lee YS, Jeong JJ, Nam KH et al. Papillary carcinoma located in the thyroid isthmus. World J Surg 2010; 34: 36–39

[3] Karatzas T, Charitoudis G, Vasileiadis D et al. Surgical treatment for dominant malignant nodules of the isthmus of the thyroid gland: a case control study. Int J Surg Lond Engl 2015; 18: 64–68

[4] Iyer NG, Shaha AR. Management of thyroid nodules and surgery for differentiated thyroid cancer. Clin Oncol (R Coll Radiol) 2010; 22: 405–412

[5] Wang J, Sun H, Gao L et al. Evaluation of thyroid isthmusectomy as a potential treatment for papillary thyroid carcinoma limited to the isthmus: a clinical study of 73 patients. Head Neck 2016; 38: 1510–1514

[6] Vasileiadis I, Boutzios G, Karalaki M et al. Papillary Thyroid Carcinoma of the Isthmus: Total Thyroidectomy or Isthmusectomy? Am J Surg 2018; 216: 135–139

[7] Polyzos SA, Kita M, Avramidis A. Thyroid nodules-stepwise diagnosis and management. Hormones (Athens) 2007; 6: 101–119

[8] Tessler FN, Middleton WD, Grant EG et al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): White Paper of the ACR TI-RADS Committee. J Am Coll Radiol 2017; 14: 587–595

[9] Hahn SY, Han BK, Ko EY et al. Ultrasound findings of papillary thyroid carcinoma originating in the isthmus: comparison with lobe-originating papillary thyroid carcinoma. Am J Roentgenol 2014; 203: 637–642

[10] Gao L, Xi X, Jiang Y et al. Comparison among TIRADS (ACR TI-RADS and KWAK-TI-RADS) and 2015 ATA Guidelines in the diagnostic efficiency of thyroid nodules. Endocrine 2019; 64: 90–96

[11] Hoang JK, Middleton WD, Farjat AE et al. Reduction in thyroid nodule biopsies and improved accuracy with American college of radiology thyroid imaging reporting and data system. Radiology 2018; 287: 185–193

[12] Basha MAA, Alnaggar AA, Refaat R et al. The Validity and Reproducibility of the Thyroid Imaging Reporting and Data System (TI-RADS) in Categorization of Thyroid Nodules: Multicentre Prospective Study. Eur J Radiol 2019; 117: 184–192

[13] Zhang B, Jiang YX, Liu JB et al. Utility of contrast-enhanced ultrasound for evaluation of thyroid nodules. Thyroid 2010; 20: 51–57

[14] Trimboli P, Castellana M, Virili C et al. Performance of contrast-enhanced ultrasound (CEUS) in assessing thyroid nodules: a systematic review and meta-analysis using histological standard of reference. Radiol Med 2020; 125: 406–415

[15] Yu D, Han Y, Chen T. Contrast-enhanced ultrasound for differentiation of benign and malignant thyroid lesions: meta-analysis. Otolaryngol Head Neck Surg 2014; 151: 909–915

[16] Kwak JY, Han KH, Yoon JH et al. Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. Radiology 2011; 260: 892–899

[17] Kim EK, Park CS, Chung WY et al. New sonographic criteria for recommending fine-needle aspiration biopsy of nonpalpable solid nodules of the thyroid. Am J Roentgenol 2002; 178: 687–691

[18] Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. Thyroid 2009; 19: 1159–1165

[19] Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid 2017; 27: 1341–1346

[20] Grani G, Lamartina L, Ramundo V et al. Taller-Than-Wide Shape: A New Definition Improves the Specificity of TIRADS Systems. Eur Thyroid J 2020; 9: 85–91

[21] Kamaya A, Tahvildari AM, Patel BN et al. Sonographic detection of extracapsular extension in papillary thyroid cancer. J Ultrasound Med 2015; 34: 2225–2230

[22] Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977; 33: 159–174

[23] Wildman-Tobriner B, Buda M, Hoang JK et al. Using Artificial Intelligence to Revise ACR TI-RADS Risk Stratification of Thyroid Nodules Diagnostic Accuracy and Utility. Radiology 2019; 292: 112–119

[24] Lauria Pantano A, Maddaloni E, Briganti SI et al. Differences between ATA, AACE ACE AME and ACR TI-RADS ultrasound classifications performance in identifying cytological high-risk thyroid nodules. Eur J Endocrinol 2018; 178: 595–603

[25] Yuan Z, Quan J, Yunxiao Z et al. Contrast enhanced ultrasound in the diagnosis of solitary thyroid nodules. J Can Res Ther 2015; 11: 41–45

[26] Zhang Y, Zhou P, Tian SM et al. Usefulness of combined use of contrast-enhanced ultrasound and TI-RADS classification for the differentiation of benign from malignant lesions of thyroid nodules. Eur Radiol 2017; 27: 1527–1536

[27] Li SY, Huang P, Cosgrove D et al. Pseudoenhancement of Gallbladder Sludge: A Confusing Artifact Caused by Nonlinear Propagation of Ultrasound Through Microbubbles. Ultraschall in Med 2016; 37: 307–309

[28] Bönhof JA, McLaughlin G. Artifacts in Sonography – Part 3. Ultraschall in Med 2018; 39: 260–283

[29] Xu Y, Qi X, Zhao X et al. Clinical diagnostic value of contrast-enhanced ultrasound and TI-RADS classification for benign and malignant thyroid tumors: one comparative cohort study. Medicine (Baltimore) 2019; 98: e14051