



# Logistic regression analysis of contrast-enhanced ultrasound and conventional ultrasound of follicular thyroid carcinoma and follicular adenoma

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**Background:** Follicular thyroid carcinoma (FTC) is prone to recurrence and hematogenous metastasis, preoperative accurate diagnosis is still needed to help clinicians select the best surgical methods to improve the prognosis of patients. The aim of this study was to find specific conventional ultrasound (US) and contrast-enhanced ultrasound (CEUS) characteristics of FTC and to explore their diagnostic value in the differential diagnosis between FTC and follicular adenoma (FA).

**Methods:** This retrospective study included 258 thyroid follicular neoplasms (172 FAs and 86 FTCs) in 244 consecutive patients who underwent preoperative conventional US, and 72 of them underwent both conventional US and CEUS. Sonograms were reviewed in consensus by two experienced radiologists for various conventional US and CEUS features. Multivariate logistic regression analysis was performed to determine independent risk factors for FTC.

**Results:** Independent risk factors of conventional US for FTC were heterogeneity (OR =7.477, 95% CI: 2.848–19.629), unevenly thick halo (OR =5.643, 95% CI: 3.234–9.848) and calcifications (OR =1.748, 95% CI: 1.098–2.783). While independent risk factors determined with the combination of CEUS and conventional US were unevenly thick halo (OR =5.770, 95% CI: 1.310–25.409) and absent or irregular rim enhancement (OR =27.000, 95% CI: 2.445–298.178). The area under the receiver operating characteristic curve of the final two logistic regression models was 0.835 and 0.838.

**Conclusions:** Conventional US is an efficient diagnostic tool in the differential diagnosis of FTC and FA to help clinicians in making appropriate decisions while CEUS failed to provide additional diagnostic value in the study, thus the value of CEUS remains to be verified by further studies with larger sample sizes.

**Keywords:** Follicular thyroid carcinoma (FTC); follicular adenoma; logistic regression; conventional ultrasound; contrast-enhanced ultrasound

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## Introduction

Thyroid cancer is the most common malignancy of the endocrine system, and it has risen significantly in recent years. The two most common histological subtypes are papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), which account for approximately 70–75% and 15–20% of all thyroid malignancies, respectively (1). As is known, most PTC have good prognosis with slow growth, while FTC is prone to recurrence and hematogenous metastasis to distant locations such as bone and lung (2). Unfortunately, intraoperative frozen-section analysis is not reliable and does not provide useful information for intraoperative decision-making (3,4). Although FTC can be confirmed postoperatively by histological observation of capsular or vascular invasion, preoperative accurate diagnosis is still needed to help clinicians select the best surgical methods to improve the prognosis of patients.

For now, the main preoperative diagnostic methods for thyroid cancer are fine needle aspiration cytology and conventional ultrasound (US). Ultrasonography (US)-guided fine needle aspiration (FNA) cytology has become the most accurate modality for preoperative definitive assessment of thyroid nodules. Follicular adenoma (FA) and FTC are thyroid neoplasms consisting of differentiated follicular cells with similar cytomorphological features (5-7). In several previous studies, when a FNA sample of a thyroid nodule reveals a follicular neoplasm, approximately 80–90% of such lesions are benign (8-10). However, most researchers still believe that thyroid malignancy cannot easily be determined in follicular neoplasms (11,12). Conventional ultrasound is the main imaging tool in the characterization of thyroid nodules, and could help clinicians determine when a nodule requires FNA or sonographic follow-up. Several sonographic features including hypoechogenicity, irregular margin, taller-than-wide shape, and microcalcification are associated with malignancy especially in PTC, but none were proved to be appropriate for FTC (13-15). Koike's prospective research reported that the sensitivity of the classic US characteristics of thyroid carcinoma was found to be 86.5% for non-follicular neoplasms, but only 18.2% for follicular carcinomas (16).

Contrast-enhanced ultrasound (CEUS) has been widely used for assessment of thyroid-related diseases, relying on differentiating background tissues acoustic response (linear) from the non-linear response of bubbles. Through observation of the microcirculation perfusion within the lesion, researchers have tried to distinguish benign from

malignant thyroid nodules with specific contrast-enhanced features (17-20). However, to the best of our knowledge, there are no studies focusing on the diagnostic value of the contrast-enhanced features in the differentiation of FTC and FA before. Furthermore, a few studies have tried to find the sonographic difference between them, but no agreement has yet been reached (21-24). In the present study, we aimed to find specific conventional US and CEUS characteristics of FTC and to explore their diagnostic value in the differential diagnosis between FTC and FA. We present the following article in accordance with the STARD reporting checklist (available at <https://dx.doi.org/10.21037/gs-21-535>).

## Methods

### Patients

We retrospectively reviewed medical records of 303 thyroid follicular neoplasms (including a histopathologic diagnosis of follicular carcinoma or follicular adenoma) which underwent conventional US before final surgery in our institution from January 2013 to August 2019. Of these nodules, 45 were excluded due to US images of unsatisfactory quality. In the end, a total of 258 thyroid follicular neoplasms in 244 consecutive patients were recruited for the study, and 72 cases of them underwent both conventional US and CEUS before surgery. Among them, there were 50 males and 194 females, aged 17–80 years, with an average age of  $48.3 \pm 15.1$  years. The mean US-measured maximum diameter of the 258 nodules was  $32.4 \pm 13.4$  mm (range, 5.0–73 mm). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital [No. 2018-KY-040 (K)] and individual consent for this retrospective analysis was waived.

### Conventional ultrasound

All sonographic examinations were performed with color Doppler ultrasound diagnostic equipments such as Acuson S2000 (Siemens, Erlangen, Germany), Mylab 90 Xvision (ESAOTE, Italy), iU Elite (Philips Healthcare, Bothell, WA), and HI Vision Preirus (Hitachi Medical, Tokyo, Japan). Line array probes were used with frequencies from 6–15 MHz. The research subject was positioned at a supine position with necks hyperextended to fully

expose the thyroid area. The following sonographic features were recorded for each nodule: maximum tumor diameter, echogenicity (hyperechoic, isoechoic, hypoechoic [with respect to the background thyroid]), echo texture (homogeneous, heterogeneous), margin (regular, irregular), border (clear, obscure), extracapsular extension (absent, present), peripheral halo sign (absent, thin, unevenly thick), cystic changes (absent, present), range of cystic changes [absent, predominantly solid (<50%), predominantly cystic ( $\geq$ 50%)], calcifications [absent, microcalcifications (calcification less than 2.0 mm in diameter), macrocalcifications or peripheral calcifications], the distribution patterns of nodule vascularity on color Doppler (predominantly intranodular vascularity, predominantly perinodular vascularity, diffuse or absent). Besides, we also recorded whether the peripheral halo in two-dimensional ultrasound was related to the observation of peripheral blood vessels in color Doppler.

### ***Contrast-enhanced ultrasound***

CEUS was performed with a linear probe of 3–9 MHz (L522) of ultrasound system (ESAOTE MyLab 90 Xvision, Italy) after Conventional US, and the sampling frame was adjusted to include the lesion and the surrounding normal tissue. As bubble disruption was strictly related to depth and focalization of a US beam, focus was placed deeper than the nodule being examined at low MI (0.05–0.07) to avoid the destruction of microbubbles. Sulphur hexafluoride (SonoVue<sup>®</sup>, Bracco International, Milan, Italy) was injected with an intravenous bolus of 1.2 mL via a 20-gauge cannula followed by a 10-mL saline flush. In the meantime, the imaging timer on the US machine was started, and each contrast imaging acquisition lasted at least 120 s was stored in the machine hard disk. The following CEUS characteristics were recorded: arrival time (time from intravenous administration to appearance of the first bubble in tumor compared with that of surrounding parenchyma), classified as earlier, synchronous or later; entrance mode of microbubble echoes [centripetal, non-centripetal (diffuse, centrifugal)]; peak intensity (hypo-enhancement, iso-enhancement, or hyper-enhancement); homogeneity of enhancement pattern at peak (homogeneous, heterogeneous); early washout compared with the adjacent thyroid parenchyma (absent, present); wash-out style (rapid, slow); perfusion defects (absent, present); range of perfusion defects (<50%,  $\geq$ 50%); rim enhancement (the rim enhancement pattern of the lesion should be thin and

regular): classified as absent or irregular, present.

All the preoperative sonograms including conventional ultrasound and CEUS were reviewed in random order on the screen by two skilled radiologists (Q Wu and Y Qu) blinded to the clinical and pathological information. Each reader independently analyzed conventional US and CEUS images first, and then reviewed the cases with discrepancy in their initial evaluation together. Finally, a consensus was reached after discussion.

### ***Statistical analysis***

Statistical analysis was performed with a statistical package (SPSS 19.0, Chicago, IL, USA). Quantitative data were expressed as the mean and standard deviation, and groups were compared using Student's *t*-test. The Chi-square test or Fisher exact test was used to compare categorical data. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using logistic regression. Only those factors found to be significantly associated with follicular carcinomas in the univariable analyses ( $P < 0.05$ ) were then included in the multivariable analysis. The variables that showed statistical correlation by logistic regression analysis were considered as independent predictive factors for follicular carcinomas. The receiver operating characteristic (ROC) analysis was performed to determine the diagnostic value of different logistic regression formulas. In all cases, two-tailed *P* values lower than 0.05 were considered to indicate statistical significance.

## **Results**

Among all 258 thyroid follicular neoplasms, 172 were follicular adenomas and 86 were follicular thyroid carcinomas which consisted of 74 minimally invasive FTCs and 12 widely invasive FTCs, and widely invasive FTC is mainly recognized due to extensive invasion by histopathology, and there were no lymph node metastases in all the FTC cases. The clinical and conventional ultrasound features of follicular adenomas and carcinomas are shown in *Table 1*. There was a significant difference in sex between research subjects with follicular carcinoma (male to female ratio, 5:12) and those with follicular adenoma (male to female ratio, 25:134) ( $P < 0.05$ ), which indicated that male patients were more common in FTC group than FA group. Other variables, such as patients' age ( $48.3 \pm 15.2$  versus  $48.3 \pm 15.0$  years), maximum tumor diameter ( $34.4 \pm 14.3$  versus  $31.4 \pm 12.9$  mm), did not show a significant difference

**Table 1** Clinical and conventional ultrasound features of FTC and FA

Feature	FTC (n=86)	FA (n=172)	P value
Age (y)	48.3±15.2	48.3±15.0	0.969
Sex	n=85	n=159	
Female	60	134	0.012
Male	25	25	
Maximum diameter (mm)	34.4±14.3	31.4±12.9	0.092
Echogenicity			0.007
Hypoechoic	40	47	
Isoechoic	45	120	
Hyperechoic	1	5	
Echo texture			<0.001
Homogeneous	7	83	
Heterogeneous	79	89	
Margin			<0.001
Regular	71	168	
Irregular	15	4	
Border			0.007
Clear	79	170	
Obscure	7	2	
Extracapsular extension			0.004
Absent	81	172	
Present	5	0	
Peripheral halo sign			<0.001
Absent	25	58	
Thin	6	109	
Unevenly thick	55	5	
Cystic changes			0.012
Absent	57	84	
Present	29	88	
Range of cystic changes			0.023
Absent	57	84	
Predominantly solid (<50%)	26	74	
Predominantly cystic (≥50%)	3	14	
Calcifications			0.004
Absent	55	140	
Microcalcifications	7	12	
Macrocalcifications or peripheral calcifications	24	20	

**Table 1** (continued)**Table 1** (continued)

Feature	FTC (n=86)	FA (n=172)	P value
Vascularity			0.001
Predominantly intranodular vascularity	11	9	
Predominantly perinodular vascularity	25	90	
Diffuse or absent	50	73	

FTC, follicular thyroid carcinoma; FA, follicular adenoma.

between FTC and FA groups (all  $P>0.05$ ).

### Conventional US

On univariable analysis, sonographic features including echogenicity, echo texture, margin, border, extracapsular extension, peripheral halo sign (91 out of 114 FA cases with peripheral halo in two-dimensional ultrasound were found peripheral blood vessels in color Doppler, while 57 out of 61 were found in FTC), cystic changes, range of cystic changes, calcifications, and nodule vascularity showed significant difference between FA and FTC (all  $P<0.05$ ). These factors were thus included in the further multivariable analysis, which identified the following independent risk factors for follicular carcinoma: hypoechoic echogenicity (OR =0.475, 95% CI: 0.232–0.971, as  $OR<1$  usually indicates that exposure is associated with lower odds of the outcome, hypoechoic echogenicity was excluded in the following study), heterogeneity (OR =7.477, 95% CI: 2.848–19.629), unevenly thick halo (OR =5.643, 95% CI: 3.234–9.848) and calcifications (OR =1.748, 95% CI: 1.098–2.783) (model 1) (Table 2). Then, the above three sonographic features were enrolled in the final multivariable logistic regression model of conventional US (model 1\*). Figure 1 show the conventional US images of follicular adenomas and carcinomas, respectively.

### CEUS

In our retrospective study, only 72 cases had undergone both conventional US and CEUS before the final surgery. The CEUS features of follicular adenomas and carcinomas are detailed in Table 3. Among the CEUS characteristics, early washout, rapid wash-out style, and absent or irregular rim enhancement showed significant associations with follicular carcinoma in the univariable analysis (all  $P<0.05$ ).

**Table 2** Multivariate logistic regression analysis

Variable	P value	Odds ratio	95% CI
Multivariate logistic regression model of conventional US			
Hypoechoic echogenicity	0.041	0.475	0.232–0.971
Heterogenicity	0	7.477	2.848–19.629
Absence of cystic changes	0.893	0.854	0.086–8.495
Irregular margin	0.059	4.539	0.946–21.790
Obscure border	0.05	9.426	1.004–88.464
Extracapsular extension	0.999	NA	NA
Unevenly thick halo	0	5.643	3.234–9.848
Range of cystic changes	0.932	1.091	0.147–8.103
Calcifications	0.019	1.748	1.098–2.783
Vascularity	0.232	1.257	0.864–1.830
Constant	0	0.016	
Multivariate logistic regression model of CEUS in combination with conventional US			
Hypoechoic echogenicity	0.213	0.342	0.063–1.852
Heterogenicity	0.998	NA	NA
Unevenly thick halo	0.02	5.77	1.310–25.409
Range of cystic changes	0.306	2.496	0.432–14.412
Calcifications	0.145	2.455	0.734–8.208
Vascularity	0.494	0.741	0.313–1.750
Early washout	0.453	0.505	0.085–3.001
Rapid washout	0.193	4.11	0.490–34.495
Absent or irregular rim enhancement	0.007	27	2.445–298.178
Constant	0.998	0	

US, conventional ultrasound; CEUS, contrast-enhanced ultrasound; CI, confidence intervals; NA, not available.

We then put the aforementioned significant CEUS features into the further multivariable analysis along with potential sonographic features (echogenicity, echo texture, peripheral halo sign, range of cystic changes, calcifications, nodule vascularity). Among all of the characteristics, independent risk factors for follicular carcinoma were: unevenly thick halo (OR =5.770, 95% CI: 1.310–25.409) and absent or irregular rim enhancement (OR =27.000, 95% CI: 2.445–298.178) (model 2) (Table 2). Then, these two factors were enrolled in the final multivariable logistic regression model

of CEUS in combination with conventional US (model 2\*). Figure 2 show the conventional gray-scale and contrast-enhanced images of follicular adenomas and carcinomas, respectively.

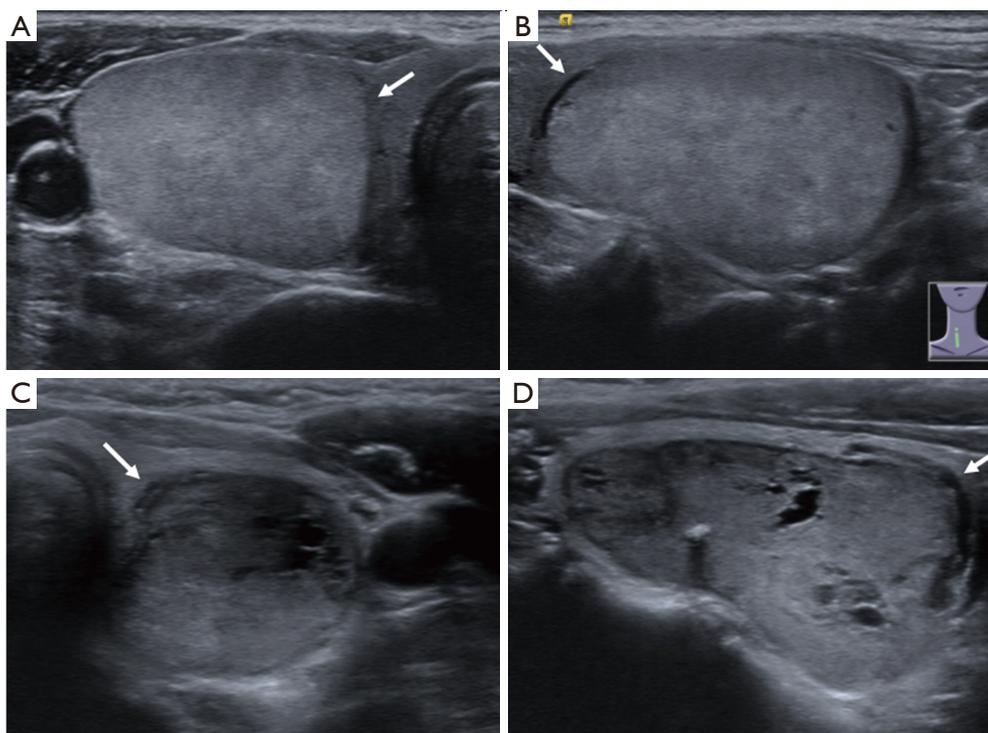
### Diagnostic performance

For the differential diagnosis between follicular adenomas and carcinomas, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of individual ultrasound features are summarized in Table 4. In the multivariable logistic regression model of conventional US, unevenly thick halo had the highest diagnostic accuracy (86.0%), with a sensitivity of 64.0%, specificity of 97.1%, PPV of 91.7% and NPV of 84.3%. While in the logistic regression model of CEUS in combination with conventional US, unevenly thick halo also had the highest diagnostic accuracy (86.1%), with a sensitivity of 68.0%, specificity of 95.7%, PPV of 89.5% and NPV of 84.9%. The absent or irregular rim enhancement showed a very high sensitivity (96%) and NPV (96%), which suggested a useful feature for ruling out follicular thyroid cancer. We further conducted ROC analysis for the final two logistic regression models to define the preoperative diagnostic value of these factors in differentiating FTC from FA. The AUC (area under the curve) of model 1\* was 0.835, and the 95% CI was 0.782–0.889, while the AUC of model 2\* was 0.838, and the 95% CI was 0.734–0.942 (Figure 3).

### Discussion

Previous studies have suggested that thyroid follicular neoplasms are more common in female, but the incidence of follicular carcinoma in male is higher than that in thyroid adenomas, and a follicular carcinoma diagnosis is said to be more often present in a larger tumor of an older patient (21,25). In the present research, we found that male patients were more common in FTC group than FA group ( $P < 0.05$ ). While older age ( $48.3 \pm 15.2$  versus  $48.3 \pm 15.0$  years) and larger tumor size ( $34.4 \pm 14.3$  versus  $31.4 \pm 12.9$  mm) were shown in follicular carcinoma group although there was no statistically significant difference (all  $P > 0.05$ ), in accordance with both Zhang and Kuo's studies (23,24). With relatively large sample size, we remain skeptical about the distribution difference of age and tumor size between FTC and FA, and further multicenter studies are necessary to validate these findings.

Heterogenicity has been reported to be associated with follicular carcinoma (OR =24.881;  $P < 0.01$ ) (23). Some



**Figure 1** Conventional US images of follicular adenoma and follicular carcinoma. (A,B) A 61-year-old female patient with follicular adenoma. Gray-scale ultrasound image shows the transverse and longitudinal views of an isoechoic and slightly heterogeneous nodule with smooth halo (white arrow) in the right lobe of the thyroid. (C,D) A 52-year-old female patient with follicular carcinoma. Gray-scale ultrasound image shows the transverse and longitudinal views of a hypoechoic and heterogeneous nodule with calcification and an unevenly-thick halo (white arrow) in the left lobe of the thyroid gland.

researchers found no significant difference in echotexture between follicular thyroid carcinoma and thyroid adenoma (23,25). Our study obtained the results similar to the former: over 90% of follicular carcinomas had heterogeneous echotexture, while thyroid adenomas appeared more homogeneous in echotexture. Presumptively, there are both follicular structures and solid proliferation with rich cell components in thyroid follicular carcinomas, which might result in different echo intensity of acoustic reflection.

Peripheral halo sign is considered as a hypoechoic ring surrounding a thyroid nodule, and its role in differentiating thyroid follicular neoplasms is still under debate. Zhang *et al.* (23) reported that the thick and uneven halo around the nodule was more common in thyroid follicular carcinoma, but it was not an independent risk factor for thyroid follicular carcinoma. While Sillery *et al.* (22) thought the halo corresponded with the well-defined capsule that surrounds follicular adenomas, and the presence of a halo sign was more frequently associated with

benign follicular neoplasia. In this study, unevenly thick halo was found to be more common in follicular carcinomas than adenomas, and it showed the highest diagnostic accuracy (86.0% and 86.1%) as an independent risk factor for follicular carcinoma (OR =5.643, 95% CI: 3.234–9.848; OR =5.770, 95% CI: 1.310–25.409) in both of the two multivariable logistic regression models. In addition, we found the halo sign was the representation of peripheral blood vessels in two-dimensional ultrasound in most cases (91/114 in FA, and 57/61 in FTC), which is consistent with the description of previous research (26); while in some other cases, color flow signal could not be detected from the halo, indicating that there might be other pathological changes for the formation of hypoechoic halo sign. Early studies have found follicular carcinomas generally have a well-defined, complete capsule with a thickness of 0.1–0.3 cm, and the capsule is composed of parallel collagenous fibers, often containing medium-sized blood vessels with irregular thickness and edema of muscular walls

**Table 3** Contrast-enhanced ultrasound features of FTC and FA

Feature	FTC (n=25)	FA (n=47)	P value
Arrival time			0.379
Earlier	17	26	
Synchronous	4	15	
Later	4	6	
Mode of entrance			0.293
Centripetal	16	24	
Non-centripetal	9	23	
Peak intensity			0.93
Hypo-enhancement	6	9	
Iso-enhancement	3	6	
Hyper-enhancement	16	32	
Homogeneity			0.554
Homogeneous	13	21	
Heterogeneous	12	26	
Early washout			0.04
Absent	6	23	
Present	19	24	
Wash-out style			0.017
Rapid	10	7	
Slow	15	40	
Perfusion defects			0.264
Absent	13	18	
Present	12	29	
Range of perfusion defects			0.674
<50%	24	44	
≥50%	1	3	
Rim enhancement			<0.001
Absent or irregular	24	23	
Present	1	24	

FTC, follicular thyroid carcinoma; FA, follicular adenoma.

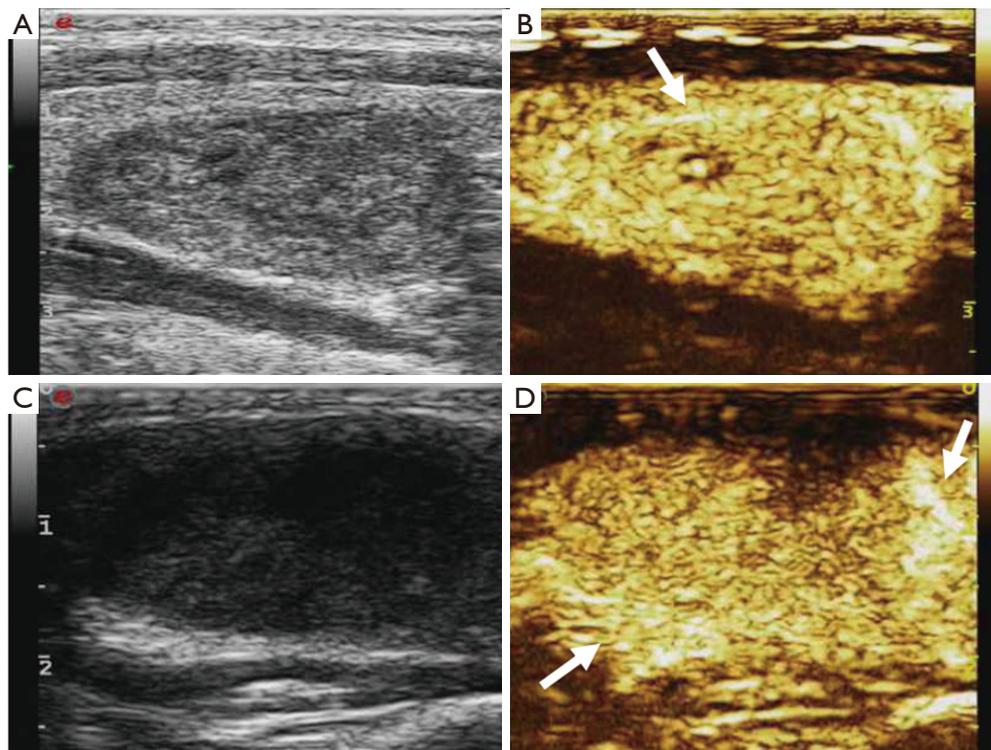
(27,28), which may help explain why the capsule tends to be thicker and more irregular in follicular carcinomas than adenomas.

Calcifications (including microcalcifications, macrocalcifications and peripheral calcifications) are common ultrasound findings within thyroid nodules.

Actually, microcalcifications have been generally recognized as an important sonographic feature for differentiating between malignant and benign nodules especially in papillary carcinoma (12,29). Nevertheless, the diagnostic value of calcification for follicular carcinoma is still unknown. In the present study, though we found the overall prevalence of calcification in the involved follicular neoplasms is at a low level, the presence of calcifications was more common in follicular carcinomas as an independent risk factor for follicular carcinoma (OR =1.748, 95% CI: 1.098–2.783) in the multivariable logistic regression model of conventional US. This point is consistent with the results reported by Zhang and Kuo *et al.* (23,24). With regard to the subgroups of calcifications in this study, microcalcification was present in small numbers (12 in FA and 7 in FTC), while macrocalcifications and peripheral calcifications were more frequently found in FTC than FA. The presence of calcifications and calcification types in follicular carcinomas might indicate the internal state of metabolic disorder, thus a further larger study is needed to find the potential pathological correlation.

The aforementioned sonographic features including heterogeneity, unevenly thick halo and calcifications were all identified as independent risk factors for follicular carcinoma in our further multivariable analysis, and the AUC of the model used to determine the probability of malignancy was 0.835 with a 95% CI of 0.782–0.889. In addition, on the basis of univariable analysis, several other sonographic features including margin, border, extracapsular extension, cystic changes, range of cystic changes, nodule vascularity differed significantly between FA and FTC. Indeed, predominantly solid, irregular margins, or chaotic arrangement of internal vascularity has been reported to be suggestive of FTC in previous studies, respectively (22,23). Even so, none of these features in the present study were confirmed as significant risk factors for follicular carcinoma, and it remains unclear whether they could help differentiate the two types of follicular neoplasms.

To the best of our knowledge, our study is the first in the radiologic literature focusing on the diagnostic value of the contrast-enhanced features in the differentiation between thyroid follicular carcinoma and thyroid adenoma. Among the contrast-enhanced characteristics, our study showed early and rapid washout without rim enhancement were more frequently present in follicular carcinomas. When these significant CEUS factors were put into the further multivariable analysis along with other potential sonographic features, the final diagnostic model displayed



**Figure 2** Conventional US and CEUS images of follicular adenoma and follicular carcinoma. (A,B) A 40-year-old male patient with follicular adenoma. Gray-scale and contrast-enhanced ultrasound image shows the longitudinal views of a hypoechoic and heterogeneous nodule with thin and regular rim enhancement (white arrow) in the right lobe of the thyroid. (C,D) A 43-year-old female patient with follicular carcinoma. Gray-scale and contrast-enhanced ultrasound image shows the longitudinal views of an extremely hypoechoic and heterogeneous nodule with irregular rim enhancement (white arrow) in the right lobe of the thyroid.

**Table 4** Performance of CEUS and conventional US characteristics in diagnosis of follicular adenomas and carcinomas

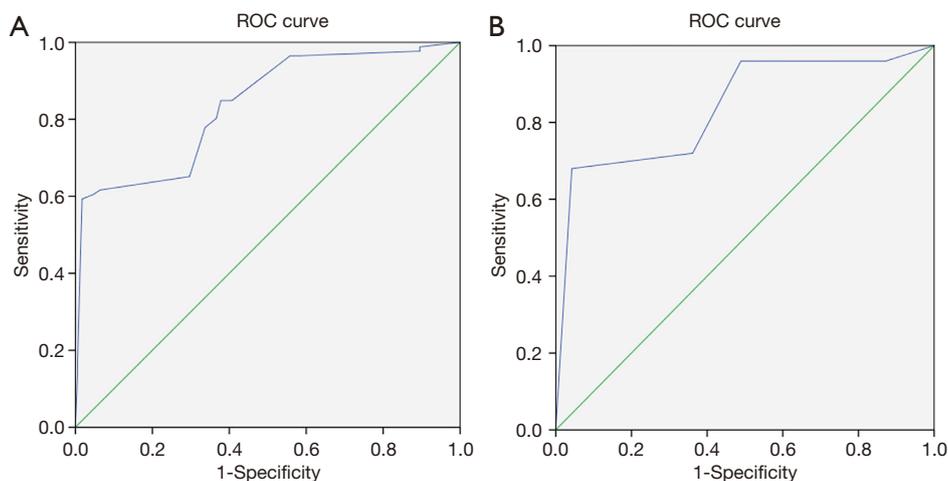
	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %
Independent risk factors for model 1*					
Heterogeneity	91.9	48.3	47	92.2	62.8
Unevenly thick halo	64	97.1	91.7	84.3	86
Calcifications	36	81.4	49.2	71.8	66.3
Independent risk factors for model 2*					
Unevenly thick halo	68	95.7	89.5	84.9	86.1
Absent or irregular rim enhancement	96	51.1	51.1	96	66.7

Model 1\* refers to the multivariate logistic regression model of conventional US, and model 2\* refers to the multivariate logistic regression model of CEUS in combination with conventional US. US, conventional ultrasound; CEUS, contrast-enhanced ultrasound; PPV, positive predictive value; NPV, negative predictive value.

good diagnostic performance with the AUC of 0.838, and only absent or irregular rim enhancement (OR =27.000, 95% CI: 2.445–298.178) and unevenly thick halo (as

aforesaid) were confirmed as independent risk factors for follicular carcinoma.

Ring enhancement has been reported as a valuable



**Figure 3** Receiver operating characteristic (ROC) curve of the final two logistic regression models for defining the preoperative diagnostic value of the factors in differentiating follicular adenomas from follicular carcinomas. The AUC (area under the curve) of multivariable logistic regression model of conventional ultrasound was 0.835 (A), while the AUC of multivariable logistic regression model of contrast-enhanced US in combination with conventional ultrasound was 0.838 (B).

indicator for benign thyroid nodules with high sensitivity and specificity (18,19), but its diagnostic role in the differentiation between thyroid follicular carcinoma and thyroid adenoma has not yet been discussed. Our study found that follicular adenoma usually exhibited thin and regular rim enhancement (may not be complete ring enhancement) on CEUS. Ring enhancement is considered to be associated with capsular and peripheral compressed parenchymal vessels around the lesion (18). Follicular adenoma often has a complete capsule, whereas capsular or vascular invasion, the typical feature of follicular carcinoma which refers to the penetration of the tumor into a vessel or capsule, might result in the absent or irregular rim enhancement.

Certainly, there are still several limitations in our study. First, the interpretive results may vary among different radiologists before operation. However, all preoperative sonograms of this study were interpreted again in random order on the screen by two experienced radiologists by consensus despite the lack of intra- and inter-observer reproducibility testing. Additionally, though early and rapid washout differ significantly in the univariable analysis, they didn't show much more significance in the further logistic regression analysis for the differential diagnosis of follicular neoplasms, and we speculate the reason for this may be related to the small sample. Indeed, because of the rarity of follicular carcinoma, the enrolled sample size in this study is rather small especially in the CEUS group. According

to daily clinical practice, we usually make a diagnosis on the basis of all the significant sonographic features, and so the combined value of conventional US and CEUS, but not the value of CEUS alone, was deemed necessary for the analysis. In the current study, since AUCs for the diagnostic models including or excluding CEUS indicated similar diagnostic value (0.838 and 0.835), it showed that diagnostic models including or excluding CEUS both had high diagnostic value indeed in the differentiation between FTC and FA. On the other hand, it seemed that CEUS did not show additional diagnostic value to help distinguish follicular neoplasms, therefore larger study is required for further observations.

## Conclusions

According to our study, follicular neoplasms with the following sonographic features including heterogeneity, unevenly thick halo and calcifications were considered highly suspicious as follicular carcinomas. While further CEUS imaging also supported the diagnosis by absent or irregular rim enhancement with good diagnostic value though it did not show additional diagnostic value to help distinguish follicular neoplasms in the current study. In conclusion, conventional US is an efficient diagnostic tool in the differential diagnosis of FTC and FA to help clinicians in making appropriate decisions while CEUS failed to provide additional diagnostic value in the study,

thus the value of CEUS in the diagnosis of benign and malignant follicular neoplasms remains to be verified by further studies with larger sample sizes.

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### Footnote

*Reporting Checklist:* The authors have completed the STARD reporting checklist. Available at <https://dx.doi.org/10.21037/gs-21-535>

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*Ethical Statement:* 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital [No. 2018-KY-040 (K)] and individual consent for this retrospective analysis was waived.

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