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Diagnostic significance of ultrasound characteristics in discriminating follicular thyroid carcinoma from adenoma

Ruifang Xu[1†], Wanwan Wen[1†], Yanning Zhang[2], Linxue Qian[1] and Yujiang Liu[1*]

Abstract

Background Follicular thyroid carcinoma (FTC) is the second most common cancer of the thyroid gland and has a greater propensity for haematogenous metastasis. However, the preoperative differentiation of FTC from follicular thyroid adenoma (FTA) is not well established. Certain ultrasound characteristics are associated with an increased risk of thyroid malignancy, but mainly for papillary thyroid cancers and not for FTC.

Objectives This retrospective study aimed to evaluate the ultrasound characteristics of FTC and the value of ultrasound characteristics in differentiating FTC from FTA.

Methods A total of 96 patients with pathologically confirmed FTC or FTA who underwent preoperative thyroid ultrasound were included in this study. The ultrasound and pathological characteristics were evaluated.

Results Our data revealed that the incidences of lesions with tubercle-in-nodule, spiculated/microlobulated margins, mixed vascularization, egg-shell calcification, central stellate scarring, extension toward the capsule and chronic lymphocytic thyroiditis were significantly higher in the FTC group (all $p < 0.05$). After adjusting for confounding factors, lesions with mixed vascularization (odds ratio [OR]: 2.038, $P = 0.019$), central stellate scarring (OR: 87.992, $P = 0.007$), extension toward the capsule (OR: 22.587, $P = 0.010$), and chronic lymphocytic thyroiditis (OR: 9.195, $P = 0.006$) were independently associated with FTC. Furthermore, combined with chronic lymphocytic thyroiditis, mixed vascularization, central stellate scarring, and extension toward the capsule showed high discriminatory accuracy in predicting FTC (AUC: 0.914; sensitivity: 96.5%; specificity: 71.8%; $p < 0.001$).

Conclusions In combination with chronic lymphocytic thyroiditis, mixed vascularization, central stellate scarring, and extension toward the capsule have greater accuracy in differentiating FTCs from FTAs.

Keywords Follicular thyroid carcinoma, Follicular thyroid adenoma, Ultrasound, Chronic lymphocytic thyroiditis

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Introduction

Thyroid nodular disease is one of the most widespread endocrine disorders. Primary thyroid carcinoma originates from follicular cells, parafollicular cells, or lymphoid components [1]. Follicular thyroid adenoma (FTA) and follicular thyroid carcinoma (FTC), as well as differentiated thyroid carcinoma, are derived from differentiated follicular epithelial cells [2]. In addition to papillary thyroid carcinoma, FTC is the most common differentiated thyroid cancer, accounting for 10–15% of thyroid carcinomas [3]. FTC has a strong tendency for blood borne dissemination and distant metastasis, particularly when it affects the lung and bone; thus, FTC is an important prognostic factor that is independently associated with poor survival in FTC patients [4, 5]. To date, accurately diagnosing FTC has been an arduous undertaking, especially in distinguishing FTC from FTA preoperatively, because they have overlapping cytomorphological features. Furthermore, the diagnosis of FTC requires histopathological proof of tumor capsule invasion and/or vascular invasion. Accordingly, diagnostic surgeries are recommended for patients presenting with suspicious follicular nodules, with the aim of evaluating the presence of capsular or vascular invasion, but the malignancy rate is quite low, leading to a large portion of suspicious follicular nodules being pathologically confirmed to be benign tumors after surgery [6, 7]. Therefore, development of a preoperative noninvasive approach that discriminates between FTC and FTA holds utmost importance, as it enables accurate detection and diagnosis of thyroid follicular tumors in clinical practice.

High-resolution ultrasound is the preferred imaging technique for assessing the morphological features of thyroid nodules. Moreover, the ultrasound guided fine needle aspiration biopsy is a commonly employed technique that can facilitate a more precise cytological diagnosis; however, it has certain limitations, particularly in distinguishing FTC from FTA [1, 2, 8]. Thus, grayscale ultrasound and color Doppler ultrasound features have extremely important clinical significance in differentiating FTC from FTA nodules. Early studies revealed that ultrasound characteristics such as taller-than-wide shape, tumor protrusion, microcalcifications or mixed type of calcifications, irregular margins, marked hypoechogenicity, and irregular shape were associated with malignant thyroid nodules [9–12]. However, only a few studies have specifically evaluated ultrasound characteristics for differentiating FTA and FTC [13, 14]. Due to the paucity of data, guidelines do not clearly specify the optimal ultrasound characteristics for monitoring patients with FTC. Therefore, it remains uncertain whether grayscale ultrasound and color Doppler ultrasound features can be used for the differentiation of FTC from FTA.

The objectives of this research were to evaluate grayscale ultrasound and color Doppler ultrasound characteristics of FTC; to identify whether pathologically confirmed chronic lymphocytic thyroiditis is associated with FTC; and to explore whether these ultrasound and pathological characteristics can distinguish FTC from FTA.

Methods

Study design and patients

This was a retrospective, observational, descriptive study that included 96 patients with pathologically confirmed FTC or FTA who underwent preoperative thyroid ultrasound and surgical resection at Beijing Friendship Hospital from September 2016 to August 2023. The inclusion criteria were as follows: (1) underwent preoperative thyroid ultrasound; (2) had pathologically confirmed FTC or FTA; (3) underwent hemithyroidectomy or total thyroidectomy; and (4) underwent lymph node dissection, which involved the removal of lymph nodes from either the central neck region, the lateral neck region, or both. The exclusion criteria were as follows: (1) follicular tumor of uncertain malignant potential; (2) histologically showing coexisting thyroid malignancies such as papillary thyroid carcinoma or medullary carcinoma; and (3) lack of a precise correlation between pathology and ultrasound findings in patients with multiple nodules. The baseline demographic information of the participants, including age and sex, was gathered. The study was approved by the Medical Ethics Committee of the Beijing Friendship Hospital (2023-P2-340). All members of our team are firmly committed to maintaining the confidentiality of patients' data and adhering to the ethical guidelines of the Declaration of Helsinki.

Ultrasound examination

Thyroid ultrasound examination was carried out scanners such as Philips iU22 or iU Elite (Philips Medical Systems, Bothell, WA, USA), GE LOGIQ E9 (GE Healthcare, Wauwatosa, WI, USA), or others equipped with a linear transducer operating at frequencies ranging from 8 to 18 MHz. To optimize the image during the examination, adjustments were made to various parameters including gain, depth, focus, edge enhancement, and dynamic range. Each thyroid lobe was imaged in the longitudinal and transverse axis. Grayscale ultrasound and color Doppler data were collected for each thyroid lobe. The following ultrasound characteristics of each thyroid nodule were documented and subsequently evaluated by two researchers who were blinded to the diagnosis: three-dimensional size, location (left/right/isthmus), echogenicity (marked hypoechogenicity/hypoechogenicity/isoechogenicity/hyperechogenicity/mixed echogenicity), internal structure (homogeneity/heterogeneity/

tubercle-in-nodule), nodular composition (mixed cystic and solid/solid), margin (spiculated or microlobulated/irregular/smooth), presence of a peripheral halo, vascularization(absent/perinodular/intranodular/perinodular or intranodular), aspect ratio (anteroposterior to transverse diameter ratio>1/<1), calcification(absent/microcalcifications /.

macrocalcifications/egg-shell), the presence of a central stellate scarring, and suspected extension toward the capsule. The three orthogonal diameters of the nodule included the largest diameter (d1) and two perpendicular diameters (d2 and d3). The nodule volume was subsequently determined via the following formula: volume=$\pi/6 \times d1 \times d2 \times d3$. The "tubercle-in-nodule" was defined as numerous nodule-like solid masses within a thyroid nodule [13]. The term "spiculated or microlobulated" was defined as spiculated, jagged or microlobulated changes in part(s) of the margin. Nodule calcification was further classified as microcalcifications (≤1 mm in diameter; exhibiting minute punctuated hyperechoic foci that may or may not cast an acoustic shadow), macrocalcifications (punctate echogenic foci>1 mm), or egg-shell calcifications (located peripherally or forming a rim). The "central stellate scarring" characteristic pertains to spoke like central scars or a network of extensions within the nodules, resembling a wheel hub and spokes. All sonographers had over five years of expertise in superficial organ ultrasound diagnosis, specializing in the differential diagnosis of thyroid conditions. Any discrepancies arising between the two researchers regarding these features were resolved through mutual agreement.

Surgery

All patients underwent surgical procedures conducted by surgeons with a decade of clinical experience, under general anesthesia. Surgical techniques and decisions were guided by the American Thyroid Association Management guidelines [1]. A transverse neck incision, ranging from approximately 5 to 8 centimeters, was made superior to the sternal notch. Prior to excision, the recurrent laryngeal nerve and parathyroid gland were carefully identified and protected. The resected thyroid nodules were subsequently fixed in formalin, embedded in paraffin, and sectioned serially at 3-millimeter thickness for subsequent hematoxylin-eosin staining and immunohistochemical analysis.

Pathology

The pathological diagnoses and classifications of follicular neoplasms were conducted by an experienced histopathologist based on the 2017 WHO Classification of Tumors of Endocrine Organs, Fourth Edition [15]. Tumors containing more than 75% Hürthle cells are categorized as Hürthle cell tumors, which are currently referred to as oncocytic tumors. FTC is a thyroid malignancy with capsular and/or vascular invasion. Based on the degree of invasion as defined by the WHO, FTC nodules can be further grouped into two categories: minimally invasive follicular carcinoma, characterized by limited vasculature penetration within tumor capsules without signs of invasion, and widely invasive follicular carcinoma, characterized by extensive infiltration of tumor capsules, blood vessels, and adjacent thyroid tissue. The histopathological indicators of chronic lymphocytic thyroiditis, extrathyroidal extension, capsular invasion, vascular invasion, lymph node metastasis, and nonlymphatic metastasis were verified through postoperative hematoxylin-eosin staining. The positive intensity and expression rate of the Ki-67, CD31, CD34, D2-40, TG, TTF-1, galectin3, and CK19 proteins in FTC were assessed via immunohistochemical analysis. The immunostaining intensity of CD31, CD34, D2-40, TG, TTF-1, galectin3, and CK19 was evaluated as follows: positive staining was defined as the presence of fine granular brown staining in ≥10% of the cells, whereas negative staining was characterized by the absence of staining or <10% cytoplasmic staining.

Statistical analysis

Statistical analyses were conducted using SPSS version 25 software (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was utilized to assess the normality of continuous variables. Normally distributed variables are represented as the means±standard deviations and were analyzed via Student's t-tests. Non-normally distributed variables are reported as the medians [25th-75th percentiles] and were analyzed with the Mann-Whitney *U* test. Categorical variables are expressed as numerals (percentages) and were compared via the chi-square test. The Spearman correlation coefficient was used to explore the correlation between the occurrence of FTC and ultrasound/pathological characteristics. Univariate and multiple logistic regression analyses (using the forced entry method) were conducted to investigate the associations between FTC and ultrasound/pathological characteristics. Additionally, receiving operator curves (ROC) were generated to predict FTC, and the area under the curve (AUC), sensitivity, and specificity of the ultrasound/pathological characteristics were recorded. An AUC of 0.5 indicated no predictive ability, whereas an AUC of 1 implied perfect prediction. A p value<0.05 was considered statistically significant.

Results

Baseline clinical and ultrasound characteristics of patients with follicular neoplasms

A total of 96 patients (aged 56 [44–64] years, including 96 with follicular neoplasms) underwent preoperative

Table 1 Baseline clinical and ultrasound characteristics of patients and follicular neoplasms

	FTC($n=57$)	FTA($n=39$)	*P* value
Baseline characteristics			
Age, years	54.0 (42.5–63.0)	57.0 (50.0–64.0)	0.173
Men, n (%)	14(24.6)	11(28.2)	0.690
Ultrasound characteristics			
Lesion volume, cm^3	9.81(3.13–27.33)	4.81(1.10-20.15)	0.178
Location, n (%)			0.409
Left	28(49.1)	15(38.5)	
Right	28(49.1)	24(61.5)	
Isthmus	1(1.8)	0(0.0)	
Echogenicity, n (%)			0.237
Marked hypoechogenicity	1(1.8)	1(2.6)	
Hypoechogenicity	36(63.2)	30(76.9)	
Isoechogenicity	2(3.5)	0(0.0)	
Hyperechogenicity	5(8.8)	1(2.6)	
Mixed echogenicity	13(22.8)	7(17.9)	
Internal structure, n (%)			0.001
Homogeneity	3(5.3)	5(12.8)	
Heterogeneity	26(45.6)	28(71.8)	
Tubercle-in-nodule	28(49.1)	6(15.4)	
Lesion composition, n (%)			0.182
Mixed cystic and solid	2(3.5)	4(10.3)	
Solid	55(96.5)	35(89.7)	
Margin, n (%)			< 0.001
Spiculated / microlobulated	23(40.4)	3(7.7)	
Irregular	31(54.4)	26(66.7)	
Smooth	3(5.3)	10(25.6)	
Peripheral halo, n (%)	7(12.3)	4(10.3)	0.761
Vascularization, n (%)			< 0.001
Absent	6(10.5)	10(25.6)	
Perinodular	2(3.5)	13(33.3)	
Intranodular	8(14.0)	1(2.6)	
Mixed	41(71.9)	15(38.5)	
Calcification, n (%)			0.019
Absent	24(42.1)	24(61.5)	
Microcalcifications	9(15.8)	6(15.4)	
Macrocalcifications	14(24.6)	8(20.5)	
Egg-shell	10(17.5)	1(2.6)	
Aspect ratio, n (%)			0.143
>1	6(10.5)	1(2.6)	
<1	51(89.5)	38(97.4)	
Central stellate scarring, n (%)	12(21.1)	1(2.6)	0.009
Extension toward the capsule, n (%)	55(96.5)	20(51.3)	< 0.001

FTC, follicular thyroid carcinoma; FTA, follicular thyroid adenoma

thyroid ultrasound for the assessment of a thyroid nodule (Table 1). Among the 96 patients with follicular neoplasms, 57 patients (59%) were diagnosed with FTC, and 39 patients (41%) were diagnosed with FTA based on histopathological examination of surgical specimens. Patients in the two groups were matched by age, and sex. Compared with the FTA group, a greater incidence of tubercle-in-nodule (49.1% vs. 15.4%, $p=0.001$) was observed in the FTC group. The presence of local irregularity margins, namely, spiculated / microlobulated margins was greater (40.4% vs. 7.7%, $p<0.001$) in the FTC group than in the FTA group. In addition, the most common ultrasound presentations of FTC in our cohort were mixed vascularization (71.9% vs. 38.5%, $p<0.001$), lesions with egg-shell calcification (17.5% vs. 2.6%, $p=0.019$), lesions with central stellate scarring (21.1% vs. 2.6%, $p=0.009$), and lesions with extension toward the capsule (96.5% vs. 51.3%, $p<0.001$). However, there were no differences in lesion volume, lesion location, lesion echogenicity, or lesion composition between the two groups (all $p>0.05$). The frequencies of lesions with peripheral halos and those that were taller than wide were also no different between the two groups. Representative ultrasound images of lesions with tubercle-in-nodule and lesions with central stellate scarring are illustrated in Fig. 1. Representative ultrasound images of lesions with egg-shell calcification are presented in Fig. 2.

Comparison of histological features between FTC and FTA

The histopathological features of FTC and FTA in this study are shown in Table 2. Nononcocytic cell tumor is a follicular neoplasm variant type, and the frequency of follicular neoplasms variant types did not differ between FTC and FTA ($p=0.76$). Only 12 (21.1%) widely invasive FTCs were found in our study. In addition, of the 57 FTC lesions, 21 (36.8%) presented with extrathyroidal extension, 57 (100%) presented with capsular invasion, and 23 (40.4%) presented with vascular invasion. Interestingly, we found that the frequency of lesions with chronic lymphocytic thyroiditis was significantly greater in the FTC group than in the FTA group (47.4% vs. 15.4%, $p=0.001$). Postoperative pathological staining revealed that two patients had lymph node metastasis and three patients had nonlymphatic metastasis (jugular vein, sternocleidomastoid, and trachea). Moreover, with respect to immunohistochemical staining for the Ki-67 protein, the mean Ki-67 index was significantly greater in the FTC group than in the FTA group (5.0 [1.3–10.0] to 1.0 (1.0–4.0), $p=0.007$).

Associations between ultrasound and pathological characteristics and FTC

As shown by correlation analyses, the FTC in all individuals was significantly positively correlated with the

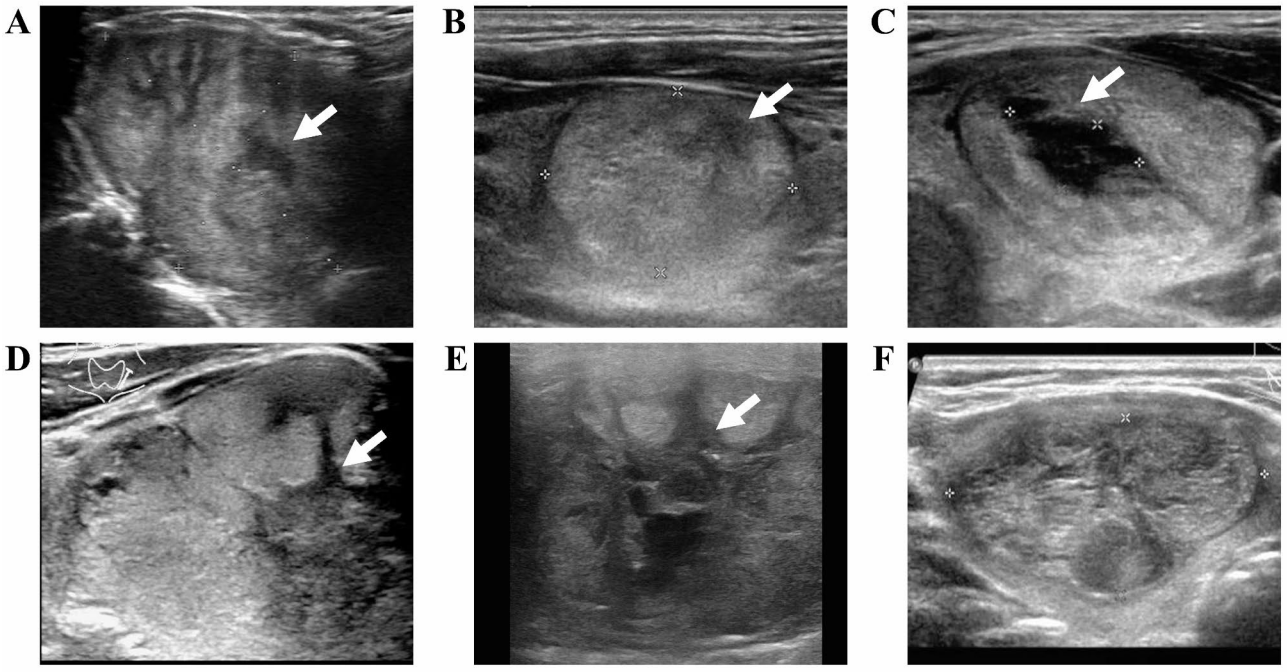

Fig. 1 Representative ultrasound images of the internal structure for follicular thyroid carcinoma. Longitudinal sonogram indicates nodules with irregular margins, hypoechoic halos and central stellate scarring (arrow) (**A**-**C**); longitudinal sonogram indicates nodules with tubercle-in-nodule and central stellate scarring (arrow) (**D**-**F**).

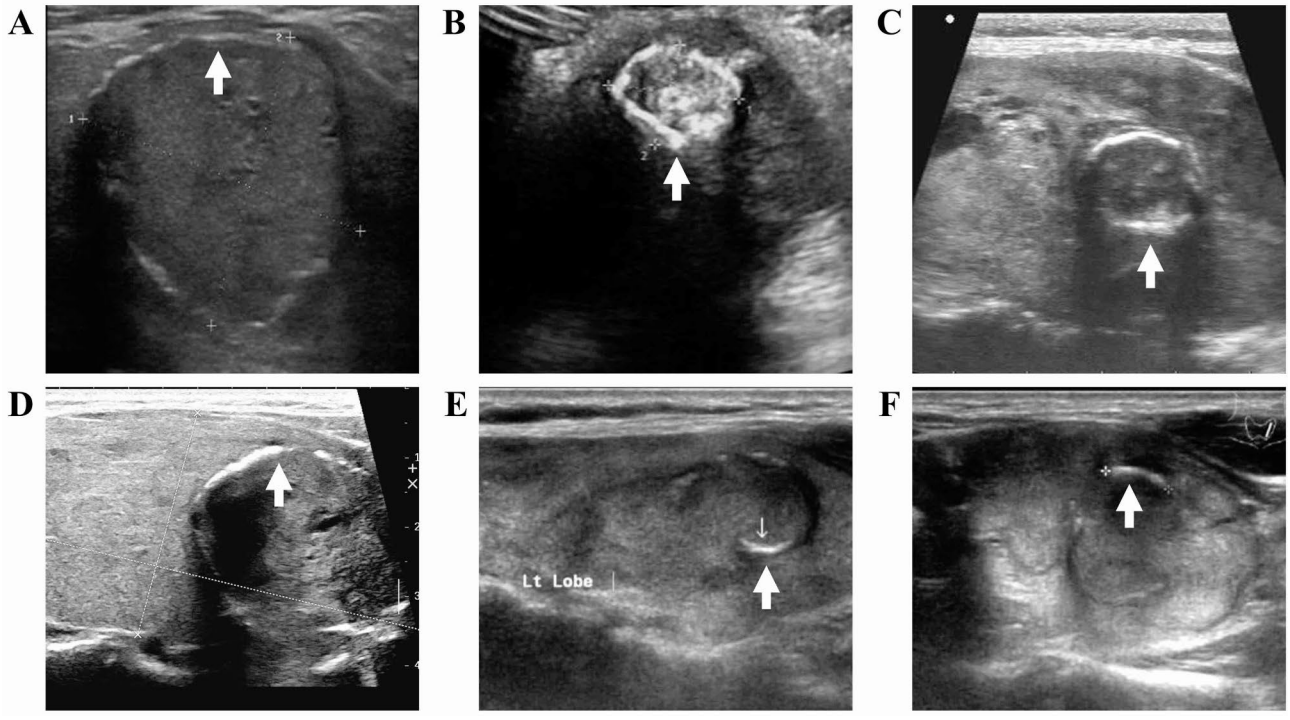

Fig. 2 Representative ultrasound images of internal calcification in follicular thyroid carcinoma. The longitudinal sonogram indicates nodules with eggshell calcification (arrow) (**A**-**D**); the longitudinal sonogram indicates nodules with macrocalcifications (arrow) (**E**-**F**)

Table 2 Pathological characteristics of FTC and FTA

	FTC($n=57$)	FTA($n=39$)	*P* value
Variant type, n (%)			0.760
Oncocytic cell tumor	7(12.3)	4(10.3)	
Nononcocytic cell tumor	50(87.7)	35(89.7)	
Histologic type, n (%)			/
Minimally invasive	45(78.9)	/	
Widely invasive	12(21.1)	/	
Extrathyroidal extension, n (%)	21(36.8)	0(0.0)	< 0.001
Capsular invasion, n (%)	57(100.0)	0(0.0)	< 0.001
Vascular invasion, n (%)	23(40.4)	0(0.0)	< 0.001
Chronic lymphocytic thyroiditis, n (%)	27(47.4)	6(15.4)	0.001
Lymph node metastasis, n (%)			0.512
Present	2(3.5)	0(0.0)	
Nonlymphatic metastasis, n (%)			0.269
Present	3(5.3)	0(0.0)	
Mean Ki-67 index, (%)	5.0(1.3–10.0)	1.0(1.0–4.0)	0.007

FTC, follicular thyroid carcinoma; FTA, follicular thyroid adenoma

Table 3 Correlation between the present of FTC and ultrasound and pathological characteristics

	Rho	*P* value
Ultrasound characteristics		
Internal structure	0.335	0.001
Margin	0.402	< 0.001
Vascularization	0.348	< 0.001
Calcification	0.216	0.024
Central stellate scarring	0.265	0.010
Extension toward the capsule	0.537	< 0.001
Pathological characteristics		
Chronic lymphocytic thyroiditis	0.331	0.001
Extrathyroidal extension	0.438	< 0.001
Capsular invasion	1.000	/
Vascular invasion	0.464	< 0.001
Mean Ki-67 index	0.362	0.007
CD31 positive	0.186	0.308
CD34 positive	0.186	0.308
D2-40 positive	0.236	0.304
TG positive	0.108	0.515
TTF-1 positive	0.229	0.226
Galectin3 positive	0.393	0.012
CK19 positive	0.335	0.032

FTC, follicular thyroid carcinoma

internal structure ($r=0.335$, $P=0.001$), margin ($r=0.402$, $P<0.001$), vascularization ($r=0.348$, $P<0.001$), calcification ($r=0.216$, $P=0.024$), central stellate scarring ($r=0.265$, $P=0.010$), and extension toward the capsule ($r=0.537$, $P<0.001$) of the lesion. Moreover, the FTC in all individuals was significantly positively associated with chronic lymphocytic thyroiditis ($r=0.331$, $P=0.001$), extrathyroidal extension ($r=0.438$, $P<0.001$), and vascular invasion ($r=0.362$, $P=0.007$). In addition, the mean Ki-67 index ($r=0.362$, $P=0.007$), positive expression of galectin3 protein ($r=0.393$, $P=0.012$), and positive expression of CK19 protein ($r=0.335$, $P=0.032$) were significantly positively correlated with FTC (Table 3). Two representative cases with FTC are illustrated in Fig. 3.

Univariate and multiple logistic regression analyses were performed to examine the associations of FTC and ultrasound and pathological variables. After adjustment confounding factors, we found that increased frequencies of lesions with mixed vascularization (odds ratio [OR]: 2.038, 95% confidence interval [CI]: 1.126 to 3.687; $P=0.019$), central stellate scarring (OR: 87.992, 95% CI: 3.333 to 2322.880; $P=0.007$), extension toward the capsule (OR: 22.587, 95% CI: 2.126 to 239.921; $P=0.010$), and chronic lymphocytic thyroiditis (OR: 9.195, 95% CI: 1.871 to 45.180; $P=0.006$) conferred a higher odds ratio of FTC (Table 4).

ROC curve analyses were performed to evaluate the predictive value of lesions with mixed vascularization, central stellate scarring, extension toward the capsule, and chronic lymphocytic thyroiditis for the identification of FTC (Fig. 4). The results showed an AUC of 0.914 (sensitivity: 96.5%, specificity: 71.8%), with a P value < 0.001, indicating that these characteristics could be predictors of FTC.

Discussion

In this study, we found that (1) the incidence of lesions with tubercle-in-nodule, spiculated/microlobulated margin, mixed vascularization, egg-shell calcification, central stellate scarring, and extension toward the capsule was significantly higher in the FTC group; (2) the frequency of lesions with chronic lymphocytic thyroiditis was significantly higher in the FTC group; and (3) the ultrasound and pathological characteristics of mixed vascularization, central stellate scarring, extension toward the capsule, and chronic lymphocytic thyroiditis were not only positively and independently associated with FTC but also highly discriminatory in predicting FTC.

FTC ranks as the second most prevalent malignant tumor of the thyroid gland, exhibiting a more aggressive nature, a heightened tendency towards haematogenous metastasis, and a shortened disease-free survival period [2, 16]. The diagnosis of FTC relies on pathological confirmation of capsular and/or vascular invasion, as FTC exhibits phenotypic and genotypic heterogeneity [17]. Therefore, the preoperative distinction between FTC and FTA remains a diagnostic challenge.

High-resolution ultrasonography of thyroid nodules is valuable for identifying significant ultrasound characteristics that aid in differentiating FTA from FTC. A recent meta-analysis encompassing twenty studies with a total of 10,215 nodules revealed that the most significant sonographic features associated with a higher risk of FTC

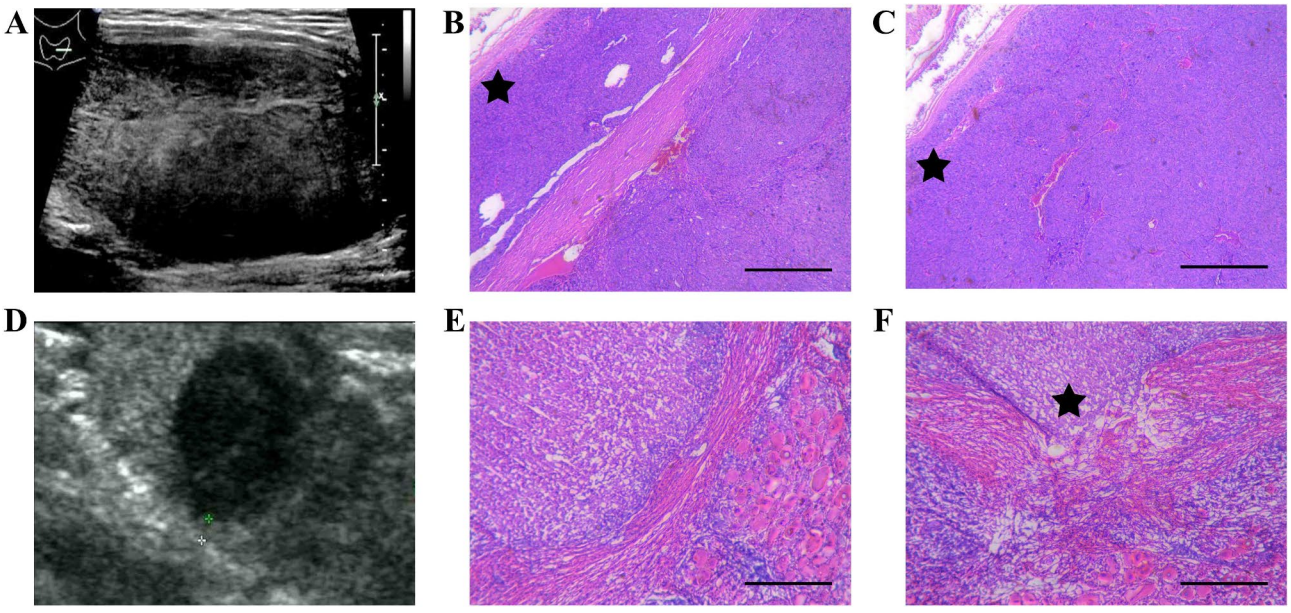

Fig. 3 Representative images of ultrasound and hematoxylin-eosin staining of specimens from patients with follicular thyroid carcinoma. Follicular thyroid carcinoma of the left thyroid in a patient. Longitudinal sonogram showing a hypoechogenicity nodule with and irregular margin and heterogeneity internal structure (**A**). Hematoxylin-eosin stain showing a satellite nodule with a secondary limiting fibrous band (star) (**B**) and tumor invasion into the hyalinized capsule (star) (**C**). Follicular thyroid carcinoma of the right thyroid in a patient. Ultrasound images showing a markedly hypoechogenicity nodule with an irregular margin and heterogeneity internal structure (**D**). Hematoxylin-eosin stain showing tumor invasion into and through the hyalinized capsule (star) (E-F) (scale bar = 500 μm)

Table 4 Association between the present of FTC and ultrasound and pathological characteristics in univariate and multiple logistic regression models

Variables	Univariate models			Multiple model		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Age, years	0.979	0.950 to 1.008	0.158	1.011	0.962 to 1.063	0.667
Sex (female vs. male)	1.207	0.480 to 3.034	0.690	1.342	0.265 to 6.808	0.722
Internal structure	3.478	1.586 to 7.630	0.002	1.141	0.265 to 4.917	0.859
Margin	5.171	2.151 to 12.428	0.000	3.842	0.984 to 15.002	0.053
Vascularization	2.015	1.378 to 2.947	0.000	2.038	1.126 to 3.687	0.019
Calcification	1.624	1.076 to 2.449	0.021	1.322	0.672 to 2.602	0.418
Central stellate scarring (no vs. yes)	10.133	1.259 to 81.534	0.029	87.992	3.333 to 2322.880	0.007
Extension toward the capsule (no vs. yes)	26.125	5.577 to 122.386	0.000	22.587	2.126 to 239.921	0.010
Chronic lymphocytic thyroiditis (no vs. yes)	4.950	1.797 to 13.637	0.002	9.195	1.871 to 45.180	0.006

FTC, follicular thyroid carcinoma; CI, confidence intervals; OR, odds ratio

were tumor protrusion, the presence of microcalcifications or mixed type calcifications, irregular margins, pronounced hypoechogenicity, and an irregular shape [10]. Consistent with this meta-analysis, we found similar high risk features, such as lesions with extension toward the capsule and spiculated/microlobulated margins. Therefore, these ultrasound characteristics have extremely important clinical implications in distinguishing follicular neoplasms.

Intriguingly, we also found that lesions with egg-shell calcification have an increased risk of FTC. Furthermore, several studies have shown that the presence of microcalcifications serves as a typical indicator of malignant thyroid tumors [13, 18, 19]. Based on nine publications covering 1199 patients, Borowczyk et al. demonstrated that the presence of not only microcalcifications but also mixed calcifications (coexisting microcalcifications and macrocalcifications) of different types was significantly associated with FTC [10]. However, in our study, thyroid nodule calcifications were further divided into microcalcifications, macrocalcifications, and egg-shell calcifications on the basis of calcification diameter and shape. We found that the proportion of egg-shell calcification was significantly higher in the FTC group than in the other groups and was significantly associated with FTC. These interesting findings implied that egg-shell calcification has extremely important differential diagnostic value in screening for FTC.

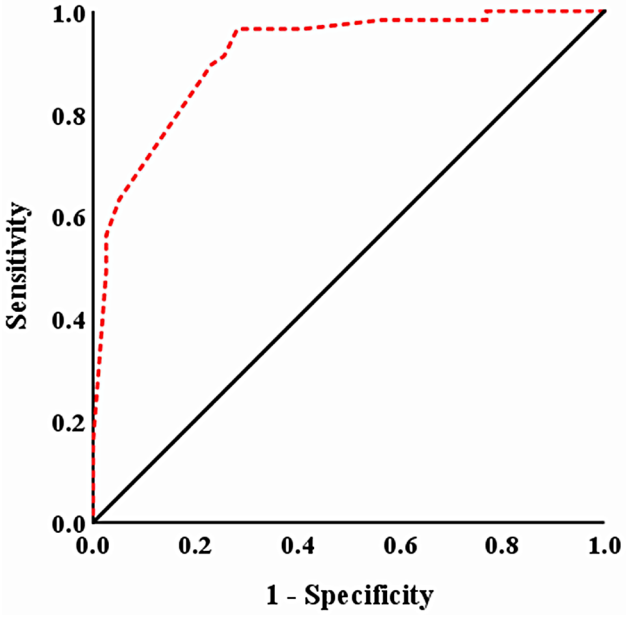

Fig. 4 Receiver operating characteristic curves using ultrasound and pathological characteristics for the prediction of follicular thyroid carcinoma. The ultrasound and pathological characteristics including mixed vascularization, central stellate scarring, extension toward the capsule, and chronic lymphocytic thyroiditis. (AUC: 0.914, 95% CI: 0.856 to 0.971, $P < 0{:}001$; sensitivity: 96.5%, specificity: 71.8%). AUC, area under the curve; CI, confidence interval

In addition, we also found that the incidence of lesions with tubercle-in-nodule and central stellate scarring was significantly higher in the FTC group than in the FTA group. There is some evidence that a solid lesion as well as heterogeneous and hypoechogenic echostructure is significantly associated with FTC [10, 20, 21]. Recent studies have suggested that the hypoechoic or markedly hypoechoic and predominantly solid patterns are correlated with significant increases in the relative risk for FTC [14, 22]. The progression and metastasis of FTC are intricately associated with various biological processes, including tumor proliferation, apoptosis dysregulation, neovascularization, neolymphogenesis, neurogenesis, epithelialmesenchymal transition, and the acquisition of metastatic capabilities [23]. Furthermore, it has been hypothesized that the ultrasound characteristics of the tubercle-in-nodule and central stellate scarring could be attributed to the rapid growth of tumor cells, leading to disrupted follicle formation, which is more characteristic of malignant lesions. Thus, the tubercle-in-nodule and central stellate scarring provided high discriminatory accuracy values for diagnosing FTC.

Furthermore, we found that the proportion of lesions with mixed vascularization significantly increased in the FCT group and was independently associated with the FTC. Earlier studies have suggested that an increase in vascularity is indicative of malignant cellular proliferation and enhances the potential for metastasis through blood vessels in malignant thyroid nodules [24, 25]. However, several studies have demonstrated that the vascularization pattern observed on Color Doppler examination is not a discriminatory feature in distinguishing between FTC and FTA [10, 20]. The most important reason for these conflicting findings may be due to different definitions of vascularization or the resolution of the ultrasonic equipment. Previous publications defined three or more vascular spots as central vascularization, but vascularization was divided into absent vascularization, perinodular vascularization, intranodular vascularization, and mixed vascularization in our study. The elevation in vascularity is typically associated with cellular proliferation under neoplastic conditions, and FTC is a well differentiated thyroid carcinoma that is more aggressive and has a greater propensity for haematogenous metastasis [1]. Thus, lesions with mixed vascularization could be a characteristic with positive diagnostic value for FTC.

Lymphocytic thyroiditis, the most prevalent form of autoimmune thyroid disease, is recognized as an independent risk factor for papillary thyroid carcinoma [26, 27]. Nevertheless, the correlations between chronic lymphocytic thyroiditis and the incidence of FTC remain poorly understood. A previous study revealed that increased serum TgAb, a marker of thyroid autoimmune pathology, was significantly associated with an increased risk of FTC [28]. Conversely, certain evidence has failed to establish a strong association between FTC and thyroid autoimmune conditions [29, 30]. However, our current study revealed that the frequency of lesions exhibiting histopathological features of chronic lymphocytic thyroiditis was notably higher in FTC lesions than in FTA lesions. And intriguingly, multiple logistic regression analysis revealed that lesions with mixed vascularization, central stellate scarring, extension toward the capsule, and chronic lymphocytic thyroiditis were independent factors. for Thus, ultrasound characteristics of chronic lymphocytic thyroiditis in combination with mixed vascularization, central stellate scarring, and extension toward the capsule help to preoperatively differentiate FTC from FA.

The strengths of this study include its rigorous inclusion criteria, histopathology, immunohistochemical diagnosis of FTC, and comprehensive data analysis. To mitigate bias, statistical adjustments were made for potential confounding ultrasound and pathological characteristics related to FTC. Nevertheless, our study has certain limitations. First, this was a retrospective observational study, and elastography or contrast-enhanced ultrasound data were not available. Second, not all FTC/FTA samples were evaluated for CD31, CD34, D2-40, TG, TTF-1, galectin3, and CK19 expression by immunohistochemical analysis. Third, our results did not

elucidate the associations between serum thyroglobulin, anti-thyroglobulin antibody, thyroid peroxidase antibodies, and thyroid stimulating hormone levels and FTC, but the histopathological signs of chronic lymphocytic thyroiditis were evaluated in our study. Future prospective, randomized, and multicenter studies with a broadened patient pool, are imperative to further investigate this topic.

Conclusion

In conclusion, we demonstrated that central stellate scarring chronic lymphocytic thyroiditis, ultrasound characteristics of mixed vascularization, central stellate scarring, and extension toward the capsule can be used to differentiate FTCs from FTAs preoperatively.

Abbreviations

AUC	Area under curve
FTA	Follicular thyroid adenoma
FTC	Follicular thyroid carcinoma
ROC	Receiving operator curves

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Author contributions

Ruifang Xu: Contributed to the conceptualization of the study, curated the data, conducted the formal analysis, secured funding, led the investigation, developed the methodology, administered the project, provided resources, utilized software, supervised the work, validated the results, created visualizations, drafted the original manuscript, and reviewed and edited the writing. Wanwan Wen: assisted in funding acquisition, conducted the investigations, validated the findings, contributed resources to the project, and reviewed and edited the manuscript. Yanning Zhang: assisted with data curation, performed formal analysis of the data, and participated in the review and editing of the writing. Linxue Qian: contributed to the formal analysis, developed the methodology, and reviewed and edited the manuscript. Yujiang Liu: provided critical feedback on the conceptualization, validated the project, and participated in the review and editing of the manuscript.

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Data availability

Upon reasonable request, the data underlying the contents of this article will be provided by the corresponding author.

Declarations

Ethics approval and consent to participate

Informed consent was waived for this study, as no human biological material was included in the project.

Consent for publication

Not applicable.

Permission to reproduce material from other sources

Not applicable.

Clinical trial number

Not applicable.

Competing interests

The authors declare no competing interests.

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