Preoperative sonographic features of follicular thyroid carcinoma predict biological behavior
A retrospective study

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Abstract

Little is known regarding biological behavior of follicular thyroid carcinomas (FTCs) according to ultrasonography features. We investigated whether there was a difference in biological behavior between benign-looking FTCs (B-FTCs) and malignant-looking FTCs (M-FTCs).

A total of 55 cases of FTC between January 2000 and December 2015 were included. B-FTCs were defined as showing none of the accepted ultrasonography criteria for malignancy, and M-FTCs were defined as showing at least one of the accepted ultrasonography criteria for malignancy. Clinicopathologic factors and sonographic features were compared between B-FTCs and M-FTCs. Based on the degree of invasiveness, FTCs were divided into minimally invasive FTCs (MI-FTCs) and widely invasive FTCs (WI-FTCs) on pathology. Sonographic features were compared between MI-FTCs and WI-FTCs.

Compared with the patients with B-FTCs (31/55, 56.4%), the patients with M-FTCs showed a significantly higher prevalence of WI-FTCs, central lymph node metastases, lateral lymph node metastases as well as extrathyroidal extension ($P < .001$, $P = .012$, $P = .031$, and $P = .032$, respectively). M-FTCs with more than one malignancy features on ultrasonography showed a significantly higher prevalence of extrathyroidal extension than M-FTCs with only one ultrasonography malignancy feature ($P = .022$). Compared with MI-FTCs (41/55, 74.5%), an irregular shape, a spiculated/microlobulated boundary, no peripheral halo ring, hypoechogenicity and microcalcification were more frequent in WI-FTCs ($P < .001$, $P = .003$, $P = .002$, $P = .015$, and $P = .016$, respectively).

Our results demonstrated that B-FTCs had better prognostic indicators than M-FTCs. Therefore, preoperative US features can serve as a useful tool for predicting biological behavior in FTC.

Abbreviations: B-FTC = benign-looking follicular thyroid carcinoma, FTC = follicular thyroid carcinoma, M-FTC = malignant-looking follicular thyroid carcinoma, MI-FTC = minimally invasive follicular thyroid carcinoma, PTC = papillary thyroid carcinoma, US = ultrasonography, WHO = World Health Organization, WI-FTC = widely invasive follicular thyroid carcinoma.

Keywords: biological behavior, follicular thyroid carcinoma, minimally invasive carcinoma, ultrasonography, widely invasive carcinoma

1. Introduction

Follicular thyroid carcinoma (FTC) accounts for approximately 10% of all thyroid malignancies and is the second most common thyroid cancer after papillary thyroid carcinoma (PTC).[1,2] However, the mortality rate of patients with FTC is higher than that of patients with PTC.[3] Some clinicopathological features can predict a more progressive course and suggest poorer prognosis, including tumor size, patient age, extrathyroidal extension, lymph node metastasis, distant metastasis, and degree of invasiveness in pathology.[4–9]

Many authors have found that preoperative thyroid ultrasonography (US) can provide useful information for differentiating FTC from benign follicular adenoma.[10,11] However, we often encounter follicular adenoma-looking masses on US that were found to have malignant histology after surgery. Because these FTCs lack accepted US criteria for malignancy, the diagnosis can be missed or delayed on US evaluation.

To our knowledge, no studies have been published to date to evaluate the previously identified biological behavior associated with US features of FTC. We hypothesized that FTC that was benign looking on US at the time of diagnosis might have better biological behavior than FTC that was obviously malignant. We investigated whether there was a difference in biological behavior between benign-looking FTCs (B-FTCs) and malignant-looking FTCs (M-FTCs).

2. Patients and methods

2.1. Patients

This study was conducted in accordance with the Declaration of Helsinki. Peking Union Medical College Hospital ethics committee approved this retrospective study and written informed consent from the participants was waived. All of the records data and sonograms were de-identified and analyzed anonymously. The records of 75 consecutive patients who underwent surgery for primary FTC confirmed by pathological examination at Peking Union Medical College Hospital between January 2000 and December 2015 were retrospectively reviewed. Preoperative sonographic findings were available for 63 patients at Peking Union Medical College Hospital. Of them, 8 patients were excluded with other variants. Ultimately, a total of 55 patients with FTCs were included in this study. In 2 patients with FTCs, there were 2 FTCs. In these 2 patients, the largest nodules were used for evaluation. Therefore, a total of 55 patients with 55 FTCs were ultimately included in this study.

2.2. Imaging and image analysis

Preoperative thyroid ultrasonography was performed in each patient using a Philips HDI, HDI5000 or iU22 (Philips Medical Systems, Bothell, WA) or GE logic 9 (GE Healthcare, Wauwatosa, WI) with a 5- to 12-MHz linear array transducer. Transverse, longitudinal and oblique plane sonograms of the thyroid and the cervical lymph nodes were obtained. Two experienced radiologists (XL and BZ) interpreted all of the preoperative sonograms by consensus. Both of the radiologists had more than 10 years of thyroid ultrasonography experience and were blind to the clinical and pathological information.

For each suspected FTC, the size, shape, margin, peripheral halo ring, echogenicity, echotexture, calcification, cystic change, and vascularity were determined. The shape was classified as regular (round or oval), taller than wide, or irregular (including lobulated). If an irregular nodule had a taller than wide shape, the shape of the nodule was categorized as taller than wide. The margin was classified as smooth, speculated, or ill-defined. The peripheral halo ring was classified as regular thin halo, irregular halo or no halo. The echogenicity was classified as marked hypoechogenicity, hypoechogenicity, isoechogenicity, or hyper-echogenicity. The echotexture was classified as homogenous or heterogeneous (including mulberry-like). Heterogeneous mulber-ry-like echotexture was defined as a feature that appeared as a conglomeration of multiple solid nodules.[12] The calcification was classified as absent, microcalcification, or macrocalcification. The cystic change was classified as present or absent. The vascularity was classified as hypervascularity (more than adjacent tissue), normal vascularity (similar to adjacent tissue) or avascularity (no blood flow).[13]

All suspected nodules were categorized into malignant or probably benign according to their US features. The malignant US features were defined as taller than wide, a speculated border, marked hypoechogenicity, or microcalcifications.[8,11,14] If a nodule had at least one of these malignant findings, it was regarded as a malignant nodule. Probably benign nodules were defined as nodules with no malignant US features. With respect to the nodule size, the largest diameter measured by US was recorded.

2.3. Pathology

According to the most recent World Health Organization (WHO) classification system, FTC was defined as an invasive neoplasm of follicular cell origin without the typical nuclear features of PTC. Based on the degree of invasiveness, the WHO classification divides FTC into minimally invasive FTC (MI-FTC) and widely invasive FTC (WI-FTC). When limited capsular and/or vascular invasion was found, the tumor was classified as MI-FTCs. When wide spread infiltration of thyroid tissue and/or blood vessels was found, the tumor was classified as WI-FTC.[15] In this study, FTCs with ≤ 3 foci of vascular invasion were classified as MI-FTCs and FTCs with >3 foci of vascular invasion were classified as WI-FTCs. Hürthle cell thyroid tumors and the follicular variant of PTC were excluded from this study.

2.4. Statistical analysis

Clinicopathologic factors (age, gender, tumor size, multifocality, WHO classification, lymph node metastasis, distant metastasis at the initial diagnosis, extrathyroidal extension, extranodal extension, and accompanying disease) and sonographic features (shape, margin, peripheral halo ring, echogenicity, echotexture, calcification, cystic change, and vascularity) were compared between B-FTCs and M-FTCs. All statistical analyses were carried out using the SPSS 11.5 software package (SPSS, Chicago, IL). Continuous variables were summarized as the means± standard deviation. Categorical variables were summarized as percentages. The chi-square test or Fisher exact test were used, as appropriate, and statistical significance was determined when a P value was <0.05.

3. Results

According to the US features, 24 tumors (43.6%) were classified as M-FTCs and 31 tumors (56.4%) were classified as B-FTCs. The clinical features of all patients are summarized in Table 1. Compared with the patients with B-FTCs, the patients with M-FTCs showed a significantly higher prevalence of WI-FTCs, central lymph node metastases, lateral lymph node metastases as well as extrathyroidal extension ($P < .001$, $P = .012$, $P = .031$, and $P = .032$, respectively). Other variables, such as patients' age, sex, tumor size, multifocality, distant metastasis at the initial diagnosis, extranodal extension, and accompanying disease, did not show a significant difference between these 2 groups (all p > 0.05).

The sonographic features of all tumors are summarized in Table 2. The common features of B-FTCs included an ovoid to round shape (100.0%), a smooth margin (100.0%), a regular thin halo ring (61.3%), hypoechoic echogenicity (54.8%), heterogeneous echotexture (71.0%), no cystic change (54.8%), no calcification (80.6%), and hypervascularity (80.6%) (Fig. 1). The common features of M-FTCs included an irregular shape (66.7%), a spiculated/microlobulated margin (41.7%), no halo ring (79.2%), hypoechoic echogenicity (66.7%), heterogeneous echotexture (75.0%), no cystic change (79.2%), microcalcifica-tion (58.3%), and hypervascularity (75.0%) (Fig. 2). There were significant differences in the shape, margin, peripheral halo ring, echogenicity, and calcification between B-FTCs and M-FTCs (all $P < .01$). There were no significant differences in the echotexture, cystic change, and vascularity (all p > 0.05).

Table 3 presents the results of analysis for the clinical manifestations of M-FTCs, according to the number of malignancy features seen on US. M-FTCs with more than one malignancy features on US showed a significantly higher prevalence of extrathyroidal extension than M-FTCs with only one US malignancy feature ($P = .022$). WI-FTCs were more common in the patients with more than one malignancy features on US than in

Table 1

Clinical characteristics of the study patients with benign-looking follicular thyroid carcinomas and malignant-looking follicular thyroid carcinomas.

Variable	B-FTCs (n=31)	M-FTCs (n=24)	Total (n=55)	*P* value
Age, years	50.3±17.1	44.7±19.3	47.9±18.2	.264
Gender (female/male)	18/13	20/4	38/17	.076
Tumor size, cm	4.0±1.9	3.1±1.7	3.6±1.9	.070
Multifocality (%)	1 (3.2)	1 (4.2)	2 (3.6)	1.000
WHO classification				<.001
MI-FTCs (%)	29 (93.5)	12 (50.0)	41 (74.5)	
WI-FTCs (%)	2 (6.5)	12 (50.0)	14 (25.5)	
Lymph node metastasis				
Central (%)	0	5 (20.8)	5 (9.1)	.012
Lateral (%)	0	4 (16.7)	4 (7.3)	.031
Distant metastasis at the initial diagnosis	1 (3.2%)	3 (12.5)	4 (7.3)	.307
Lung	1 (3.2)	2 (8.3)	3 (5.5)	.575
Bone	1 (3.2)	3 (12.5)	4 (7.3)	.307
Extrathyroidal extension (%)	2 (6.5)	7 (29.2)	9 (16.4)	.032
Extranodal extension (%)	1 (3.2)	2 (8.3)	3 (5.5)	.575
Pathologic association				
Hashimoto's thyroiditis (%)	2 (6.5)	5 (20.8)	7 (12.7)	.220
Follicular thyroid adenoma (%)	0	2 (8.3%)	2 (3.6%)	.186
Papillary thyroid carcinoma (%)	0	1 (4.2)	1 (1.8)	.436
Parathyroid adenoma (%)	0	2 (8.3%)	2 (3.6%)	.186

B-FTC = benign-looking follicular thyroid carcinoma, M-FTC = malignant-looking follicular thyroid carcinoma, MI-FTC = minimally invasive follicular thyroid carcinoma, WHO = World Health Organization, WI-FTC = widely invasive follicular thyroid carcinoma.

Table 2

Comparison of sonographic features between benign-looking follicular thyroid carcinomas and malignant-looking follicular thyroid carcinomas.

Sonographic features	B-FTCs (n=31)	M-FTCs (n=24)	Total (n=55)	*P* value
Shape				<.001
Ovoid to round (%)	31 (100.0)	8 (33.3)	39 (70.9)	
Taller than wide (%)	0	0	0	
Irregular (%)	0	16 (66.7)	16 (29.1)	
Margin				<.001
Smooth (%)	31 (100.0)	8 (33.3)	39 (70.9)	
Spiculated/microlobulated (%)	0	10 (41.7)	10 (18.2)	
Ill-defined (%)	0	6 (25.0)	6 (10.9)	
Peripheral halo ring				<.001
Absent (%)	10 (32.3)	19 (79.2)	29 (52.7)	
Regular thin halo ring (%)	19 (61.3)	2 (8.3)	21 (38.2)	
Irregular halo ring (%)	2 (6.5)	3 (12.5)	5 (9.1)	
Echogenicity				.001
Marked hypoechoic (%)	0	6 (25.0)	6 (10.9)	
Hypoechoic (%)	17 (54.8)	16 (66.7)	33 (60.0)	
Isoechoic (%)	14 (45.2)	2 (8.3)	16 (29.1)	
Echotexture				.771
Homogeneous (%)	9 (29.0)	6 (25.0)	15 (27.3)	
Heterogeneous (%)	22 (71.0)	18 (75.0)	40 (72.7)	
Cystic change				.087
Absent (%)	17 (54.8)	19 (79.2)	36 (65.5)	
Present (%)	14 (45.2)	5 (20.8)	19 (34.5)	
Calcification				<.001
No calcification (%)	25 (80.6)	4 (16.7)	29 (52.7)	
Microcalcification (%)	0	14 (58.3)	14 (25.5)	
Macrocalcification (%)	6 (19.4)	6 (25.0)	12 (21.8)	
Vascularity				.881
Avascularity (%)	2 (6.5)	2 (8.3)	4 (7.3)	
Normal vascularity (%)	4 (12.9)	4 (16.7)	8 (14.5)	
Hypervascularity (%)	25 (80.6)	18 (75.0)	43 (78.2)	

B-FTC = benign-looking follicular thyroid carcinoma, M-FTC = malignant-looking follicular thyroid carcinoma.
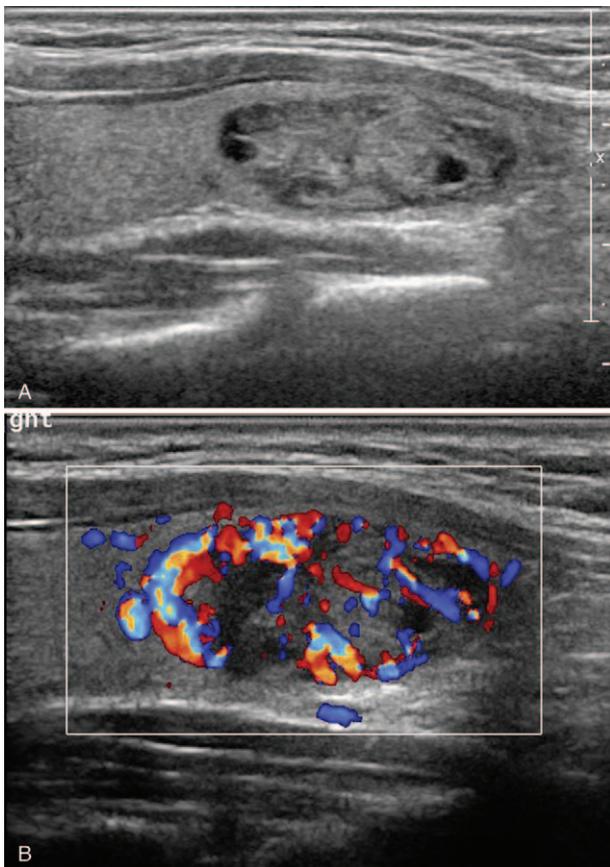
Figure 1. A 27-year-old male patient with benign-looking follicular thyroid carcinoma. (A) The gray scale sonogram shows a regular shape, a smooth margin, no peripheral halo ring, heterogeneous isoechogenicity, no calcification and partly cystic change. (B) The color Doppler sonogram shows hypervascularity.
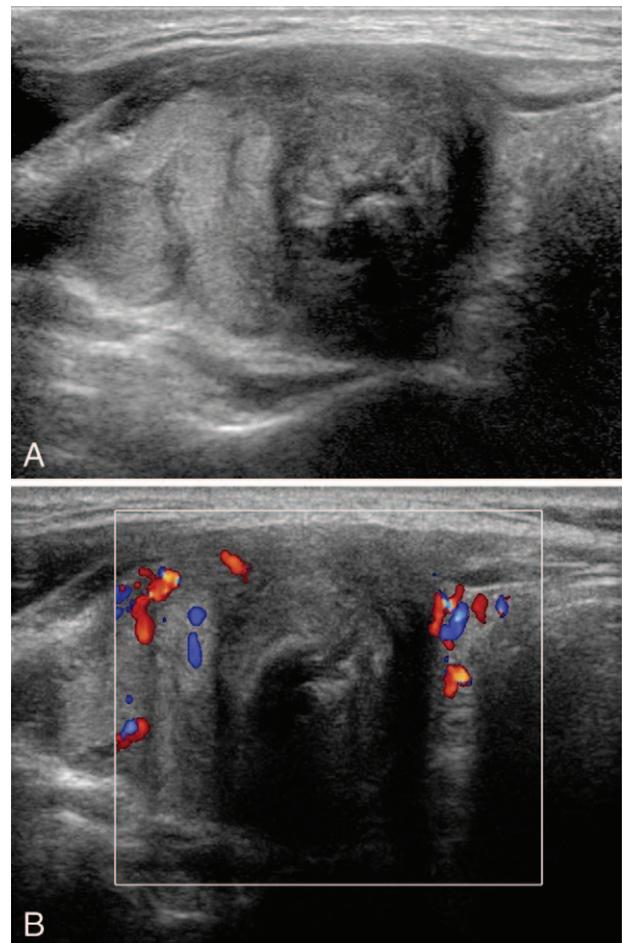
Figure 2. A 61-year-old male patient with malignant-looking follicular thyroid carcinoma. (A) The gray scale sonogram shows an irregular shape, an ill-defined margin, no peripheral halo ring, heterogeneous hypoechogenicity and isoechogenicity, microcalcification and no cystic change. (B) The color Doppler sonogram shows focal hypervascularity and focal avascularity.

those with only one US malignancy feature. However, the difference was not statistically significant ($P = .089$).

The sonographic features between MI-FTCs and WI-FTCs are summarized in Table 4. Most WI-FTCs had an irregular shape (71.4%), no peripheral halo ring (92.9%), hypoechoic echogenicity (78.6%), no cystic change (78.6%), and hypervascularity (71.4%). Most MI-FTCs had a regular shape (85.4%), a smooth boundary (82.9%), hypoechogenicity (53.7%), a heterogeneous echotexture (78.0%), no cystic change (61.0%), no calcification (63.4%), and hypervascularity (80.5%). There was no significant difference in the echotexture, cystic change, and vascularity between MI-FTCs and WI-FTCs. However, an irregular shape (71.4% vs 14.6%), a spiculated/microlobulated boundary (42.9% vs 9.8%), no peripheral halo ring (92.9% vs 39.0%), hypoechogenicity (78.6% vs 53.7%), and microcalcification (50.0% vs 17.1%) were more frequent in WI-FTCs ($P < .001$, $P = .003$, $P = .002$, $P = .015$, and $P = .016$, respectively).

4. Discussion

FTC has a propensity for hematogenous spread, and 10% to 15% of patients with FTC will present with metastatic disease, most commonly involving the lung followed by bone.[7] Although some authors have reported a benign course of minimally invasive FTCs (MI-FTCs) with low risk of tumor recurrence and distant metastases,[3,16,17] some authors have reported that

MI-FTC can also lead to distant metastases.[18] In addition, most authors have reported that WI-FTC has a worse prognosis than MI-FTC and needs more aggressive surgical procedures with radioactive iodine (^{131}I) therapy.[4,6,9] Therefore, it will be very helpful to identify patients with poor prognosis using easily accessible variables.

Our study demonstrated that the biological behavior of B-FTCs differed significantly from those of M-FTCs. Although the tumor size of M-FTCs was similar to that of B-FTCs, M-FTC patients had a greater frequency of WI-FTCs, central lymph node metastases, lateral lymph node metastases as well as extrathyroidal extension, which have been described as significant prognostic factors. Furthermore, as the number of malignant US features increased, extrathyroidal extension was more likely. These findings strongly suggest that B-FTC has a less progressive character than M-FTC. Interestingly, previous studies have demonstrated similar results in PTCs and medullary thyroid carcinomas.[8,19,20]

As a preoperative diagnostic tool, US findings can serve as important differentiating factors. Many authors have found that the US features of follicular adenoma and FTC were very similar, but larger lesion size, lack of a sonographic halo, hypoechoic appearance, the presence of calcifications, and the absence of cystic change favored a FTC diagnosis.[10,11] In this study,

Table 3

Analysis of the clinical manifestations of malignant-looking follicular thyroid carcinoma according to the number of malignancy features seen on ultrasonography.

Variable	One malignancy features (n=9)	More than one malignancy features (n=15)	P value
WHO classification			.089
MI-FTCs (%)	7 (77.8)	5 (33.3)	
WI-FTCs (%)	2 (22.2)	10 (66.7)	
Lymph node metastasis			
Central (%)	2 (22.2)	3 (20.0)	1.000
Lateral (%)	2 (22.2)	2 (13.3)	.615
Distant metastasis at the initial diagnosis	2 (22.2)	1 (6.7)	.533
Extrathyroidal extension (%)	0	7 (46.7)	.022
Extranodal extension (%)	0	2 (13.3)	.511

M-FTC = malignant-looking follicular thyroid carcinoma, MI-FTC = minimally invasive follicular thyroid carcinoma, WHO = World Health Organization, WI-FTC = widely invasive follicular thyroid carcinoma.

B-FTCs accounted for 31 (56.4%) of all 55 FTCs. These FTCs lacked US findings typical of malignancy, and failed to be diagnosed with malignant nodules on initial US evaluation. The common features of B-FTCs were found to be an ovoid to round shape, a smooth margin, a regular thin halo ring, hypoechoic echogenicity, heterogeneous echotexture, no cystic change, no calcification, and hypervascularity. Therefore, when a nodule has benign features, it may require extensive histologic sampling before they can be distinguished from follicular adenoma, because invasion of adjacent thyroid parenchyma in FTC may be grossly apparent or only limited to microscopic foci of capsular or vascular invasion.[21]

US has been widely used in clinical, including joint and blood vessel US.[22,23] Though US has been used as a first-line diagnostic tool of thyroid nodules, it has some limitations.[24] First, US is an operator dependent procedure. Second, the deep anatomic structures may acoustically shadowed by bone or air.[24] Third, routine US cannot reliably exclude minor extrathyroidal extension.[25] Hence, some researchers have looked for other diagnostic tool of thyroid nodules, such as magnetic resonance imaging. Many authors have found that magnetic resonance imaging can be used for differentiating malignant from benign thyroid nodules and cervical lymph nodes.[26,27] Song et al[28] found that magnetic resonance imaging before surgery had the

Table 4

Comparison of sonographic features between minimally invasive follicular thyroid carcinomas and widely invasive follicular thyroid carcinomas.

Sonographic features	MI-FTCs (n=41)	WI-FTCs (n=14)	Total (n=55)	P value
Shape				<.001
Ovoid to round (%)	35 (85.4)	4 (28.6)	39 (70.9)	
Taller than wide (%)	0	0	0	
Irregular (%)	6 (14.6)	10 (71.4)	16 (29.1)	
Margin				.003
Smooth (%)	34 (82.9)	5 (35.7)	39 (70.9)	
Spiculated/microlobulated (%)	4 (9.8)	6 (42.9)	10 (18.2)	
Ill-defined (%)	3 (7.3)	3 (21.4)	6 (10.9)	
Peripheral halo ring				.002
Absent (%)	16 (39.0)	13 (92.9)	29 (52.7)	
Regular thin halo ring (%)	20 (48.8)	1 (7.1)	21 (38.2)	
Irregular halo ring (%)	5 (12.2)	0	5 (9.1)	
Echogenicity				.015
Marked hypoechoic (%)	3 (7.3)	3 (21.4)	6 (10.9)	
Hypoechoic (%)	22 (53.7)	11 (78.6)	33 (60.0)	
Isoechoic (%)	16 (39.0)	0	16 (29.1)	
Echotexture				.169
Homogeneous (%)	9 (22.0)	6 (42.9)	15 (27.3)	
Heterogeneous (%)	32 (78.0)	8 (57.1)	40 (72.7)	
Cystic change				.334
Absent (%)	25 (61.0)	11 (78.6)	36 (65.5)	
Present (%)	16 (39.0)	3 (21.4)	19 (34.5)	
Calcification				.016
No calcification (%)	26 (63.4)	3 (21.4)	29 (52.7)	
Microcalcification (%)	7 (17.1)	7 (50.0)	14 (25.5)	
Macrocalcification (%)	8 (19.5)	4 (28.6)	12 (21.8)	
Vascularity				.697
Avascularity (%)	3 (7.3)	1 (7.1)	4 (7.3)	
Normal vascularity (%)	5 (12.2)	3 (21.4)	8 (14.5)	
Hypervascularity (%)	33 (80.5)	10 (71.4)	43 (78.2)	

MI-FTC = minimally invasive follicular thyroid carcinoma, WI-FTC = widely invasive follicular thyroid carcinoma.

potential to discriminate tumor aggressiveness in patients with PTC. However, whether magnetic resonance imaging can be used for differentiating WI-FTC from MI-FTC needs further investigation. Çam et al. compared US, contrast-enhanced computed tomography, and diffusion magnetic resonance imaging in differentiating between benign and malignant thyroid nodules, and found that the sensitivities and specificities of contrast-enhanced computed tomography and diffusion magnetic resonance imaging appeared relatively low.[29] Although diffusion magnetic resonance imaging has many clinical applications, such as chest, orbital and breast tumors, the value of this technique in thyroid needs more investigations.[30–32] Perfusion computed tomography has been widely used in the monitoring of head and neck cancer.[33] However, the major concern of this technique is the risk of exposure to ionizing radiation.[33] This risk limits the application of perfusion computed tomography in thyroid nodules.

There are some limitations in this study. First, this study is a retrospective study, and it is impossible to evaluate the sonography findings in real-time. Therefore, the interpretive results may vary among different radiologists. However, all preoperative sonograms of this study were interpreted by 2 experienced radiologists by consensus. Second, because of the rarity of FTC, the sample size in this study is small.

In conclusion, we demonstrated that there were significant differences in biological behavior between patients with B-FTCs and those with M-FTCs. The patients with M-FTCs showed a significantly higher prevalence of WI-FTCs, central lymph node metastases, lateral lymph node metastases as well as extrathyroidal extension. Therefore, preoperative US features can serve as a useful tool for predicting biological behavior in FTC.

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