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Follicular variant of papillary thyroid carcinoma: Gray-scale and Doppler sonographic features

Tiroid papiller karsinom folliküler varyantı: Gri-skala ve Doppler sonografik özellikleri

Tülay Öztürk[1] Süha Süreyya Özbek[1] Gülgün Demirpolat Kavukçu[1] Yeşim Ertan[2] Müge Tunçyürek[2] Ali Veral[2] Deniz Nart[2] Recep Gökhan İçöz[3] Mehmet Mahir Akyıldız[3] Özer Makay[3]

[1]Ege University Faculty of Medicine, Department of Radiology, İzmir, Turkey

[2]Ege University Faculty of Medicine, Department of Pathology, İzmir, Turkey

[3]Ege University Faculty of Medicine, Department of Surgery, İzmir, Turkey

Abstract

Aim: The aim of this study was to present the sonographic characteristics of follicular variant of papillary thyroid carcinoma (FVPTC) related to different forms of the thyroid nodules, including those without a capsule. Another purpose was to analyze the color Doppler ultrasonography (CDUS) features of this unique tumor, which have not been intensively studied in previous works.

Materials and Methods: Twenty-two thyroid nodules (male/female: 17/5; mean age±SD: 42±16 years; range: 17-70) diagnosed with FVPTC were included in this study. The sonographic and Doppler features of the nodules were analyzed retrospectively. The intranodular pattern of vascularity was categorized with regard to the presence of perinodular and/or intranodular vascular signals, as well as a “spoke-and-wheel” appearance.

Results: The length of the nodules varied from 6 to 55 mm. Most of nodules were purely solid (77.3%), isoechoic (59.1%) or hypoechoic (31.8%) and had an oval shape (72.7%), well-defined margins (68.2%) and a peripheral hypoechoic halo (68.2%). Thirty-one percent of the nodules had a lobulated shape with microlobulated margins or an irregular configuration with ill-defined margins. Encapsulated FVPTCs had a peripheral hypoechoic halo and well-defined margins, whereas infiltrative cases exhibited the opposite characteristics. No calcification was observed in 72.7% of the nodules. Perinodular and predominantly peripheral intranodular hypervascularity was observed in 14 nodules (66.7%) and was the dominant pattern of vascularity in most of the encapsulated FVPTCs, unlike the infiltrative FVPTCs.

Conclusion: Diagnosis of FVPTC should always be considered when large thyroid nodules with predominantly solid echo-texture and other sonographic features that suggest benignity and nodular hypervascularity are observe.

Keywords: Thyroid carcinoma, papillary thyroid carcinoma, follicular variant, Doppler.

Öz

Amaç: *Bu çalışmanın amacı, kapsülsüz formları da dahil olmak üzere tiroid papiller karsinom folliküler varyantının (TPKFV) farklı formlarının sonografik özelliklerini sunmaktır. Başka bir amaç ise bu nadir tümörün önceki çalışmalarda incelenmemiş olan renkli Doppler ultrasonografi (RDUS) özelliklerini analiz etmektir.*

Gereç ve Yöntem: *TPKFV tanısı alan 22 tiroid nodülü çalışmaya dahil edildi (erkek/kadın: 17/5; ortalama yaş±SD: 42±16 yıl; yaş aralığı: 17-70). Nodüllerin sonografik ve Doppler özellikleri retrospektif olarak analiz edildi. İntranodüler kanlanma paterni sınıflandırıldı. Perinodüler ve/veya intranodüler kanlanma varlığı “araba tekerleği” görünümü olarak tanımlandı.*

Bulgular: *Nodüllerin boyutu 6-55 mm arasında değişmekteydi. Nodüllerin çoğu tamamen solid (%77.3), izoekoik (%59.1) veya hipoekoik (%31.8), oval şekilli (%72.7), iyi sınırlı (%68.2) ve periferik hipoekoik haloluydu (%68.2). Nodüllerin yüzde %31’i mikrolobüle sınırlı lobule şekilli veya belirsiz sınırlı düzensiz şekilliydi. Enkapsüle TPKFV formların iyi sınırlı ve periferik hipoekoik halolu olduğu görülürken infiltratif formların ise tam tersi özellikler gösterdiği saptandı. Nodüllerin %72.7’sinde kalsifikasyon saptanmadı. 14 nodülde (%66.7) perinodüler ve ağırlıklı olarak periferik intranodüler kanlanma paterni gözlenmiş olup bu patern infiltratif TPKFV formlardan farklı olarak enkapsüle TPKFV formların çoğunda görülen dominant kanlanma paternidir.*

Corresponding Author: Tülay Öztürk

Ege University Faculty of Medicine, Department of Radiology, İzmir, Turkey

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Sonuç: *Ağırlıklı olarak solid iç yapıda olan, benign sonografik özellikler ve nodüler kanlanma paterni gösteren büyük boyutlu tiroid nodüllerinde TPKFV tanısı, her zaman düşünülmelidir.*

Anahtar Sözcükler: *Tiroid karsinomu, papiller tiroid karsinomu karsinom, folliküler variant, Doppler.*

Introduction

The most common malignancy of the thyroid gland is papillary thyroid carcinoma (PTC). Multiple variants of PTC have been reported with distinct histopathological features. The follicular variant of papillary thyroid carcinoma (FVPTC) is the second most common variant and comprises 9-22% of all PTC nodules (1). As a unique tumor, FVPTC presents with dual histopathologic characteristics. In addition to having specific nuclear features that suggest the diagnosis of PTC, FVPTC also presents with a predominant follicular pattern mimicking other follicular neoplasms (2). FVPTC is seen relatively frequently in younger populations and tends to form larger thyroid nodules. Local lymph node metastasis is rarer than PTC, whereas the clinicopathologic features are relatively favorable (3). Liu et al. (4) reported lower rates of extrathyroideal extension, positive margins and regional lymph node metastasis in patients with the encapsulated form, and no distant metastasis or recurrence of this form was observed in their series.

FVPTC, especially the encapsulated form, presents with benign imaging features as in follicular adenomas and carcinomas, with which it has similar genetic alterations and biological behavior. These facts account for why diagnosing encapsulated FVPTC and differentiating it from other tumors with a follicular pattern is a difficult task, both in cytological and sonographic studies, unlike the infiltrative form that has a more malignant appearance (5). The reported and relatively benign findings in the literature related to FVPTC are most likely due to the encapsulated form (6-8). In this study, we aimed to present the ultrasonographic characteristics of FVPTC related to different forms of the thyroid nodules, including those without a capsule. Another purpose was to analyze the color Doppler ultrasonography (CDUS) features of this unique tumor, which have not been intensively studied in previous work.

Materials and Methods

This study was approved by the local research ethics committee. Twenty-two patients with the histopathologic diagnosis of FVPTC were retrospectively evaluated. Only the largest FVPTC (“dominant FVPTC” in case of multiplicity) in each patient was enrolled in the study. The size, echogenicity, homogeneity, shape and marginal patterns, the presence or absence of any peripheral halo, internal structure, cystic component or calcification was noted. In addition, the pattern of vascularity was categorized with respect to the presence and degree of perinodular and/or intranodular vascular signals. The nodules exhibiting circumscribing perinodular vessels with multiple centripetal vascular branches were accepted to have a “spoke-and-wheel” appearance in accordance with the relevant literature (9).

The US examinations were performed between 2006 and 2013 using one of three high-resolution Doppler US units (Sonoline Antares, Acuson Antares, Acuson S2000; all by Siemens Medical Solutions USA Inc., Mountain View CA, USA) equipped with tissue harmonic and spatial compound imaging technologies. The examinations were carried out using the following high-resolution, multiple linear-array transducers: VFX 9-4 (4-9 MHz), VFX 13–5 (5-13 MHz), 14L5 (5-14 MHz), 18L6 HD (5.5-18 MHz). All examinations were performed by the same radiologist (SSO), with more than 20 years of experience on medical US applications.

Sixteen of the 22 patients underwent US guided fine-needle aspiration biopsy (FNAB) before surgery. All patients underwent total thyroidectomy based on the results of preoperative tests, intraoperative exploration and frozen section analysis (10). The nodules were subdivided into three forms as *encapsulated*, if the nodule was surrounded by a capsule; *circumscribed*, if the nodule was non-encapsulated and non-infiltrative; *infiltrative*, if the nodule was non-encapsulated but yielded signs of infiltration to adjacent thyroid parenchyma.

Intraclass correlation coefficient (ICC) was used to evaluate the agreement between the sonographic and histopathologic measurements of the longest diameter of each nodule. For this purpose, intraclass correlation coefficient according to the two-way mixed effects model was calculated.

Results

Twenty two thyroid nodules in 22 patients (male/female: 17/5; mean age±SD: 42±16) with the histopathologic diagnosis of FVPTC constituted the study group. The demographic characteristics of the patients, the time interval between the final US examination and surgery, and the pathological data of FVPTC nodules were summarized in Table-1.

US guided FNAB was performed in 16 (72.7%) patients before surgery. Cytopathologic diagnosis was *benign* in 8 nodules (50% of those biopsied), “non-diagnostic” in two nodules, “suspicious for PTC” in five nodules and “malignant” in one nodule. Although some nodules had a

cytopathologic diagnosis of benignity, all patients in the series underwent surgical excision due to suspicious sonographic findings and/or some cytopathological details.

On histological examination, all nodules had classical nuclear features of PTC with a predominantly follicular growth pattern, suggesting the diagnosis of FVPTC (Figure-1).

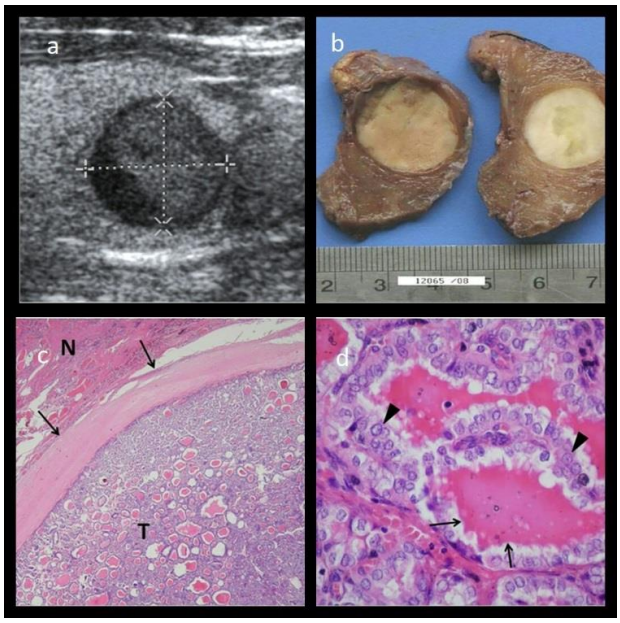

Figure-1. FVPTC in a 47 year-old female patient. **a)** Longitudinal sonogram of left thyroid lobe shows a 10-mm-long, minimally heterogeneous, hypoechoic, solid nodule with well-defined margins and hypoecoic halo. **b)** Macroscopic view of the related thyroidectomy specimen demonstrates the nodule to be a solid nodule with well-defined margins and close similarity to its sonographic appearance. **c)** Photomicrograph displays the tumor (T) with a marked capsule (arrows) and adjacent non-neoplastic tissue (N). **d)** A high-power view demonstrates a predominantly follicular pattern with follicular structures, in addition to characteristic nuclear features of PTC such as dense, pink-staining colloid (arrows), neoplastic irregular, clear nuclei with grooves and micronucleolus (arrowheads).

The longest diameter of the 21 dominant FVPTC nodules ranged between 8 and 50 mm (20±11 mm; mean±SD). The longest diameter of a FVPTC nodule which had been excised in another medical center and consulted by our pathology department was not available. The dominant FVPTC nodules had an average longest diameter of 23±12 mm (mean±SD; ranging from 6 to 55 mm) according to preoperative US examination. These measurements correlated perfectly with those obtained during histopathologic evaluations. The ICC between the sonographic and histopathologic measurements of the longest diameters of the nodules was 0.952 (95% CI, 0.865-0.983) indicating high level of agreement. The histopathologic evaluation of 22 nodule specimens revealed a capsule surrounding 15 of the FVPTC nodules (68.2%, "*encapsulated form*"). Three of the seven nodules without a capsule had circumscribed margins, one of which had focal and minimal peritumoral infiltration (all accepted as "*circumscribed form*"). The remaining four FVPTCs had invaded the adjacent thyroid parenchyma in an infiltrative pattern ("*infiltrative form*").

In 9 patients, there were additional foci of malignant nodules in the thyroid gland (Table-1). Eight of them were shown to have FVPTC nodule(s) that were smaller than the dominant FVPTC nodule, with one case having an extra focus of PTC in the classical type. The remaining patient had a classical type PTC in addition to a FVPTC nodule.

Gray-scale US and CDUS features were summarized in Table-2,3 and 4. Inner structure was purely solid in 77.3% and heterogeneous in 63.6% of the nodules (Figure-2).

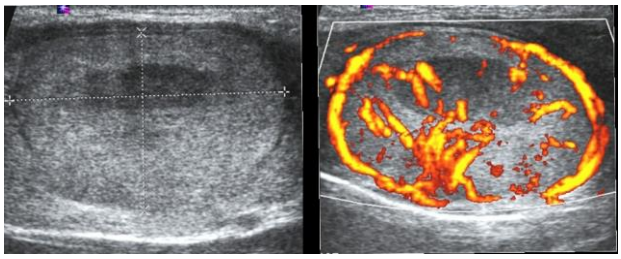

Figure-2. Typical sonographic features of a FVPTC that was discovered incidentally in a 30 year-old female patient. **a)** Longitudinal sonogram of the right thyroid lobe showing a 35-mm-long, minimally heterogeneous, oval-shaped, well-defined, and completely solid nodule with smooth margins and a centrally located, relatively hypoechoic area. There is no calcification within the mass. **b)** CDUS image of the nodule displays vessel distribution partly resembling a "spoke-and-wheel" appearance.

Cystic components of small size were present in only 5 nodules. Although two thirds of the nodules had an oval shape, well-defined margins and peripheral hypoechoic halo (Figure-2,3), there were nodules that had a lobulated shape with microlobulated margins or irregular configuration with ill-defined margins (Figure-4,5).

Table-1. The Demographic, Surgical and Pathological (Dominant FVPTC) Data of the Patients With the Diagnosis of FVPTC.

Case Initials	Age	Gender	Cyto-pathologic result	Time interval between last US examination and surgery (days)	Longest diameter in histopathologic examination (mm)	Histopathologic form	Additional malignant nodule(s) [longest diameter(s)]
1	29	F	Not performed	33	50	Encapsulated	Contralateral 1 FVPTC(4 mm)
2	30	F	Benign	84	30	Encapsulated	Contralateral 1 FVPTC(2 mm)
3	31	F	Not performed	9	15	Encapsulated	None
4	26	F	Benign	133	NA	Encapsulated	None
5	47	F	Suspicious for PTC	21	8	Encapsulated	None
6	67	M	Non-diagnostic	54	27	Encapsulated	None
7	51	F	Not performed	20	18	Encapsulated	None
8	58	M	Non-diagnostic	129	8	Encapsulated	Ipsilateral 1 FVPTC (1 mm)
9	22	F	Suspicious for PTC	107	25	Encapsulated	None
10	48	F	Benign	57	11	Encapsulated	Ipsilateral 1 FVPTC (NA)
11	35	M	Not performed	6	15	Encapsulated	Contralateral 3 PTCs (30, 15 and 5 mm)
12	17	F	Benign	7	9	Encapsulated	None
13	70	F	Benign	260	20	Infiltrative	Ipsilateral 1 FVPTC (5 mm) Contralateral 2 PTCs (microscopic)
14	34	F	Not performed	28	15	Infiltrative	None
15	65	F	Benign	69	23	Circumscribed	None
16	54	F	Suspicious for PTC	7	35	Circumscribed (with focal infiltration)	None
17	42	F	Not performed	91	23	Infiltrative	Ipsilateral 1 FVPTC (21 mm) Contralateral 3 FVPTC (8, 5 and 5 mm)
18	49	M	Suspicious for PTC	32	12	Circumscribed	None
19	47	F	Benign	182	21	Encapsulated	Contralateral 2 FVPTC (2 and 3 mm) Isthmic 1 FVPTC (3 mm)
20	51	M	Suspicious for PTC	79	12	Infiltrative	None
21	22	F	Benign	25	30	Encapsulated	None
22	31	F	Malign	29	17	Encapsulated	Ipsilateral 1 FVPTC (2 mm)

Table-2. The Sonographic Data of Dominant FVPTC Nodules in the Series.

Case Initials	Longest diameter (mm)	Shape	Margins	Echo texture	Halo	Echogenicity	Calcification	Cystic component	Vascularization pattern	"Spoke-and-wheel" appearance
1	55	Oval	Well-defined	Heterogenous	+	Isoechoic	-	-	+++	+
2	33	Oval	Well-defined	Heterogenous	+	Isoechoic	-	+	+++	+
3	15	Lobulated	Microlobulated	Heterogeneous	-	Isoechoic	+	+	+++	-
4	40	Lobulated	Microlobulated	Homogeneous	+	Isoechoic	-	+	NA	NA
5	10	Oval	Well-defined	Heterogeneous	+	Hypoechoic	-	-	+++	+
6	29	Oval	Well-defined	Homogeneous	+	Hyperechoic	+	-	++	-
7	25	Oval	Well-defined	Heterogeneous	+	Isoechoic	-	-	+++	-
8	6	Irregular	Ill-defined	Heterogeneous	-	Hypoechoic	+	-	++	-
9	26	Oval	Well-defined	Heterogeneous	+	Isoechoic	-	+	++	-
10	15	Oval	Well-defined	Homogeneous	+	Hypoechoic	-	-	+++	+
11	17	Oval	Well-defined	Homogeneous	+	Isoechoic	-	-	+++	+
12	12	Oval	Well-defined	Homogeneous	+	Isoechoic	-	-	+++	+
13	21	Irregular	Ill-defined	Heterogeneous	-	Hypoechoic	+	-	++	-
14	12	Irregular	Ill-defined	Heterogeneous	-	Hypoechoic	+	-	++	-
15	25	Oval	Well-defined	Homogeneous	-	Isoechoic	-	-	+++	+
16	27	Oval	Well-defined	Heterogeneous	+	Isoechoic	-	-	+++	+
17	25	Oval	Well-defined	Heterogeneous	+	Hyperechoic	-	-	+++	-
18	13	Lobulated	Microlobulated	Homogeneous	-	Hypoechoic	-	-	+++	-
19	31	Oval	Well-defined	Heterogeneous	-	Hypoechoic	+	-	+++	-
20	14	Oval	Microlobulated	Heterogeneous	+	Isoechoic	-	-	+++	+
21	37	Oval	Well-defined	Heterogeneous	+	Isoechoic	-	+	++	-
22	20	Oval	Well-defined	Homogeneous	+	Isoechoic	-	-	++	-

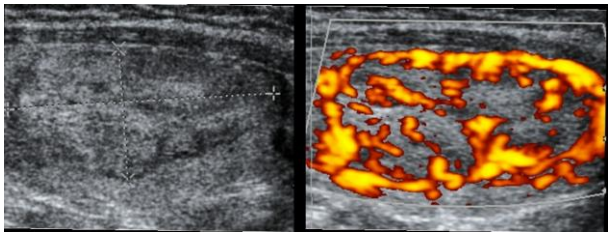

Figure-3. Circumscribed FVPTC without capsule in a 54 year-old female patient. **(a)** The oval, well-defined nodule has a maximum dimension of 27 mm, and hypoechoic halo around it. **b)** CDUS image demonstrates perinodular and predominantly peripheral intranodular hypervascularization.

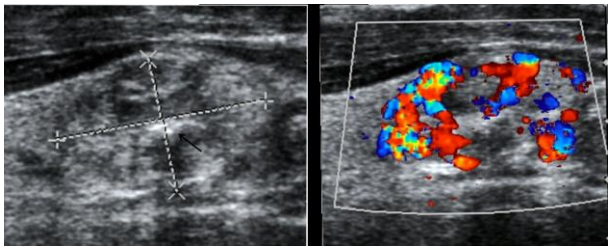

Figure-4. Course calcified foci in a FVPTC of a 31-year-old female patient. **a)** Longitudinal sonogram of right lobe demonstrates a 15-mm-long, dominantly isoechoic nodule with mixed echotexture, microlobulated borders and foci of coarse calcification (arrow). **b)** Color Doppler US image of the same nodule yields perinodular and predominantly peripheral intranodular hypervascularization.

Most of the observed nodules were isoechoic or hypoechoic compared to the normal thyroid parenchyma. Nearly 72.7% of the nodules had no calcification, whereas coarse calcification were observed in three nodules and microcalcific foci in three nodules (Figure-4,5). Only one dominant FVPTC nodule in the series was shown to have an anteroposterior diameter greater than its transverse diameter. On CDUS examination, peri- and intranodular vascular signals were demonstrated in 21 nodules. Apparent perinodular and predominantly peripheral intranodular hypervascularity was observed in 14 nodules (66.7%) (Figure-3,4). A "spoke-and-wheel" appearance was demonstrated in 9 nodules (Figure-2). The remaining 7 nodules (33.3%) were shown to exhibit rare perinodular and peripherally located intranodular vascular signals.

The sonographic features demonstrated in different forms of FVPTC are presented and compared in Table-5. Although there were exceptions in each group, the encapsulated FVPTCs typically had a peripheral hypoechoic halo and well-defined margins, whereas the infiltrative FVPTCs exhibited the opposite characteristics. The majority of the encapsulated FVPTCs, and all of the circumscribed nodules were oval in shape and isoechoic in internal appearance, contrary to the infiltrative nodules. All of the FVPTCs in the series were completely solid, except for 5 encapsulated nodules with small cystic components.

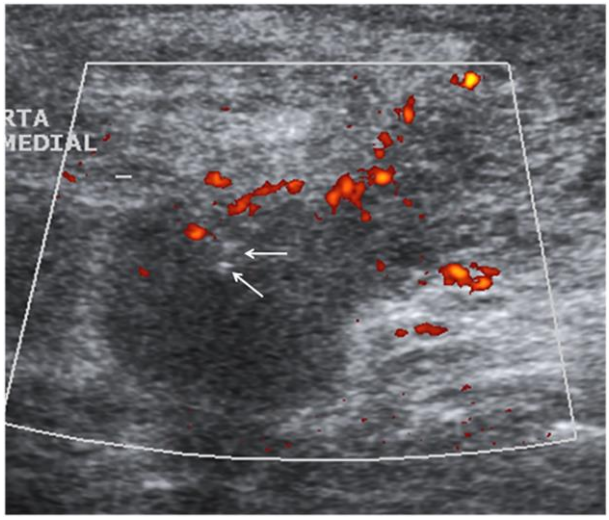

Figure-5. An infiltrative FVPTC nodule in a 70 year-old female patient. Longitudinal sonogram of left thyroid lobe demonstrates an irregular solid nodule with a long diameter of 21 mm, ill-defined margins, microcalcified foci (arrow) and rare vascular signals in its peripheral regions.

Table-3. General Overview of Gray-Scale Sonographic Features of Dominant FVPTC Nodules.

Sonographic findings	Number (%)
Shape	
Oval	16 (72.7%)
Lobulated	3 (13.6%)
Irregular	3 (13.6%)
Margin	
Well-defined	15 (68.2%)
Microlobulated	4 (18.2%)
Ill-defined	3 (13.6%)
Echo texture	
Homogeneous	8 (36.3%)
Heterogeneous	14 (63.6%)
Hypoechoic halo	
Present	15 (68.2%)
Absent	7 (31.8%)
Echogenicity	
Hypoechoic	7 (31.8%)
Isoechoic	13 (59.1%)
Hyperechoic	2 (9.1%)
Calcification	
Microcalcification	3 (13.6%)
Macrocalcification	3 (13.6%)
No calcification	16 (72.7%)
Internal content	
Purely solid	17 (77.3%)
Predominantly solid	5 (22.7%)

Forty percent of the encapsulated FVPTCs and two of the three circumscribed FVPTCs had a homogeneous echo texture, whereas all of the infiltrative legions were heterogeneous. Rare microcalcific foci were demonstrated in one of the 12 encapsulated FVPTCs and in half of the infiltrative FVPTCs. Coarse calcifications were observed in only 3 encapsulated FVPTCs within the whole series. Perinodular and predominantly peripheral intranodular hypervascularity

was the dominant pattern of vascularity in 64% of the encapsulated FVPTCs and in all of the circumscribed nodules. On the other hand, half of the infiltrative FVPTCs exhibited a similar vascularity, whereas the remaining half had rare perinodular and peripheral intranodular vascular signals. Only one of the infiltrative FVPTCs was demonstrated to have a "spoke-and-wheel" pattern of vascularization, whereas nearly half of the encapsulated nodules and all of the circumscribed nodules exhibited this appearance.

Table-4. General Overview of Doppler Sonographic Features of Dominant FVPTC Nodules.*

Vascularization pattern in Doppler evaluation	
Perinodular and predominantly peripheral intranodular hypervascularity	14 (66.7%)
Rare perinodular and peripheral intranodular vascular signals	7 (33.3%)
"Spoke-and-wheel" appearance	
Present	9 (42.9%)
Absent	12 (57.1%)

*****Percentages were calculated for the 21 cases, whose Doppler US data could be retrieved.

Table-5. The Comparison of US Findings in FVPTC Nodules With and Without Capsule.

Sonographic feature	**Encapsulated FVPTCs (number)**	**FVPTCs with circumscribed margins (number)**	**Infiltrative FVPTCs (number)**
Shape	Oval (12) Irregular (1) Lobulated (2)	Oval (2) Irregular (0) Lobulated (1)	Oval (2) Irregular (2) Lobulated (0)
Hypoechoic halo	Absent (3) Present (12)	Absent (2) Present (1)	Absent (2) Present (2)
Margin	Well-defined (12) Microlobulated (2) Ill-defined (1)	Well-defined (2) Microlobulated (1) Ill-defined (0)	Well-defined (1) Microlobulated (1) Ill-defined (2)
Internal content	Solid (10) Cystic components (5)	Solid (3) Cystic components (0)	Solid (4) Cystic components (0)
Echo texture	Homogeneous (6) Heterogeneous (9)	Homogenous (2) Heterogeneous (1)	Homogenous (0) Heterogeneous (4)
Echogenicity	Hypoechoic (4) Isoechoic (10) Hyperechoic (1)	Hypoechoic (1) Isoechoic (2) Hyperechoic (0)	Hypoechoic (2) Isoechoic (1) Hyperechoic (1)
Calcification	Absent (11) Microcalcifications (1) Coarse calcifications (3)	Absent (3) Microcalcifications (0) Coarse calcifications (0)	Absent (2) Microcalcifications (2) Coarse calcifications (0)
Vascularization pattern*	Perinodular and predominantly peripheral intranodular hypervascularity (9) Rare perinodular and peripheral intranodular vascular signals (5)	Perinodular and predominantly peripheral intranodular hypervascularity (3) Rare perinodular and peripheral intranodular vascular signals (0)	Perinodular and predominantly peripheral intranodular hypervascularity (2) Rare perinodular and peripheral intranodular vascular signals (2)
"Spoke-and-wheel" appearance*	Absent (8) Present (6)	Absent (1) Present (2)	Absent (3) Present (1)

Discussion

It was reported that marked hypoechogenicity, microlobulated or irregular margins, foci of microcalcification, a taller-than-wide shape, signs of invasion to surrounding tissue, local lymphadenopathies, and rich intranodular vascularity at CDUS were suggestive for malignancy in thyroid nodules (6-8). Although the sensitivity of these US features is relatively high for papillary and medullary carcinomas, follicular neoplasms and FVPTCs tend to display US characteristics often common to benign nodules, including a solid echo-texture, circumscribed margins, hypoechoic halo and oval shape. Microcalcifications are not regularly demonstrated in follicular tumors or FVPTC (11). Recently, the misleading "benign" US appearance

of FVPTC was held responsible for the delay of clinical suspicion of FVPTC (12). Also in our series, the majority of FVPTC nodules presented with features suggesting a false diagnosis of benignity. The exceptions were the three nodules with irregular shape and ill-defined margins. The remaining carcinomas, however, had a completely benign appearance. Therefore, there is a strong need to develop other US parameters for clinical practice.

Typically, nodules with a follicular pattern tend to present with relatively large nodules (12). Indeed, the nodules in our series were large with a mean long-diameter of 23 mm, reaching up to 55 mm. It was noteworthy that only one of 22 dominant FVPTC nodules had an anteroposterior diameter larger than its transverse dimension. The results of this study are in contradiction to the claim that the "taller-than-wider-sign" has the highest diagnostic odds ratio for malignancy (13). Another remarkable and common feature of the FVPTC nodules in our series was the relatively dominant solid texture with regard to their huge dimensions. FVPTC nodules were completely solid in 77% of our cases and had only tiny cystic components in the remaining ones, suggestive of a follicular pattern. Nodules of a follicular nature often lack cystic elements or have very small cystic components relative to their large body (14,15). That notable observation of predominantly solid content was valid for not only the encapsulated or circumscribed FVPTCs but also the infiltrative nodules in our series.

In a recent review, moderate, rich, predominant, or exclusive internal flow on CDUS of thyroid follicular neoplasms (FN) were grouped and designated as "predominant internal flow" pattern. This pattern was considered indicative of malignancy. It was reported that the overall sensitivity of CDUS was 85% [16]. De Nicola et al. reported a significant and positive association between a predominantly central flow and malignancy in thyroid FNs (17). Flow patterns of cases in these two studies show similarities to our cases described as having perinodular and predominantly peripheral intranodular flow patterns. We believe that the diversity regarding vascularity patterns is due to its description and that our classification of flow patterns is more detailed and sensitive. In the majority of our FVPTC cases, hypervascularization in the nodules was apparent, with a perinodular and predominantly peripheral intranodular distribution of vessels. It was noteworthy to observe the distribution of peripheral vessels with centripetal branches resulting in a "spoke-and-wheel" appearance in half of the nodules evaluated by CDUS, similar to that previously described for follicular tumors (9).

In the literature, the sensitivity of FNAB for diagnosis of PTC was reported to be between 75 and 94%, whereas the sensitivity of FNAB for diagnosis of FVPTC was low, varying from 25 to 37% (18-22). Cytological diagnosis of FVPTC with FNAB is more difficult than that of PTC nodules, not only because of overlapping cytomorphological features of benign and malignant follicular cells but also due to relatively small areas suggesting PTC components with focal areas of characteristic nuclear features (22-26). The authors also emphasized the importance of awareness for the possibility of FVPTC, particularly in large thyroid nodules, even in the setting of a benign FNAB (26). The aforementioned literature data also accounts for the false-negative "benign" results in 8 of the 16 nodules that had undergone cytological examination in our series, with only one of them being diagnosed as "malignant".

The major limitations of the presented study include the limited number and spectrum of the pathologic subvariants in the study group, as well as the study's retrospective design. Due to the relative scarcity of this specific pathologic entity, the instances of the FVPTCs, and especially those without capsule, are far from being adequate for a reliable statistical analysis and a solid conclusion. Such instances would be of greater significance in the case of a prospective and larger study in which the sonographic features of different forms of FVPTC nodules were compared not only to each other but also to those of other thyroid malignancies.

Conclusion

Although some subvariants may have apparent malignant US features, FVPTC nodules appear to have gray-scale and Doppler sonographic features largely identical with those of follicular thyroid neoplasms in most cases, probably due to their unique clinical and histopathological characteristics. Diagnosis of FVPTC should always be considered probable among other pathologies with a follicular pattern when large thyroid nodules with completely or predominantly solid echotexture, in addition to other typical US features suggesting benignity, are observed. The presence of perinodular and intranodular hypervascularization, especially with an accompanying "spoke-and-wheel" appearance, may further support the diagnosis.

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