

Gray-Scale and Color Doppler US Features Corresponding to Histological Subtypes of Papillary Thyroid Carcinoma¹

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Purpose: To compare the gray-scale and color or power Doppler ultrasonographic (US) features according to the histological subtypes of a papillary thyroid carcinoma (PTC).

Materials and Methods: The gray-scale and color or power Doppler US features of 159 surgically confirmed PTC (classic type of PTC, 69; classic type of papillary microcarcinoma [PMC], 67; and follicular variant of PTC [FVPTC], 23) in 118 patients were analyzed retrospectively. The following US characteristics were evaluated: the type of vascularization, echogenicity, outline, ratio of anteroposterior/transverse (AP/T) diameters, as well as the presence or absence of halo signs, cystic changes, and microcalcification.

Results: The most common type of vascularization was penetrating or central (75.4%) for the classic type of PTC, avascular (56.7%) for PMC, and peripheral and central (82.6%) for FVPTC. The echogenicity was most commonly hypoechoic (47.8%) for the classic type, hypoechoic (74.6%) for PMC, and isoechoic (30.4%) for FVPTC. The outline was most often irregular (60.9%) for the classic type, irregular (86.6%) for PMC, and regular (91.3%) for FVPTC. The ratio of the AP/T diameters was 1.0 or more in 31.9%, 55.2%, and 13.0%, a halo sign was observed in 30.4%, 6.0%, and 78.3%, cystic changes was present in 1.4%, 0%, and 21.7%, and microcalcifications were present in 55.1%, 28.4%, and 13.0% of those with the classic type, PMC, and FVPTC, respectively.

Conclusion: The gray-scale and color Doppler US features corresponding to the histological subtypes of PTC are significantly different from one another. The US features of FVPTC appear to be significantly different from the other subtypes in that they tend to have more benign US characteristics than those of the classic type or PMC.

Index words : Thyroid, neoplasms

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It has been estimated that 40% to 50% of the asymptomatic population will have a thyroid nodule that is found incidentally on ultrasonography (US). However, the overall likelihood that a given thyroid nodule is malignant is approximately 5% to 6.5% (1 - 3). Many reports have been concerned with differentiating benign from malignant lesions of the thyroid gland without considering the histological types of thyroid carcinoma (4, 5). The imaging features of follicular neoplasms, i.e. follicular adenoma and follicular carcinoma, may be different from those of the classic type of PTC in that they frequently have a regular outline (6). In addition, the US features associated with an increased risk of thyroid cancer, including the presence of calcification, marked hypoechogenicity, irregular outline, and an absence of halo (7), are frequently absent in follicular neoplasms. Therefore, before attempting to differentiate between benign and malignant thyroid lesions, it is appropriate to classify thyroid tumors into two architectural patterns, i.e., papillary and follicular. The imaging findings of the subtypes of PTC also may differ significantly from one another. However, to the best of our knowledge, there are few reports on the US features corresponding to the histological subtypes of PTC (8).

This study compared the characteristic gray-scale and color or power Doppler US features according to the subtypes of PTC i.e. classic type of PTC, classic type of papillary microcarcinoma (PMC), and FVPTC.

Materials and Methods

Patients

This retrospective study included 159 surgically confirmed PTC (classic type, 69; PMC, 67; and FVPTC, 23) in 118 patients (108 women and 10 men, age ranging from 20 to 75 years with a mean age of 45.2 years), who underwent a US examination at our hospital between January 2003 and November 2005. A small PTC measuring 10 mm or less in the maximal diameter was defined as a papillary microcarcinoma according to the World Health Organization (WHO) classification (9). All the patients provided written, informed consent, and approval was obtained from the Institutional Review Board to carry out this retrospective study.

US Examinations and Interpretation

Two investigators (SKL, SW) performed the gray-scale and color or power Doppler US examinations on all patients using a high-resolution real-time scanner (either

Sequoia 512, Acuson, Mountain View, CA, USA; or HDI-5000, Philips Medical system, Bothell, WA) equipped with a commercially available 8 - 15 MHz (Sequoia) or 5 - 12MHz (HDI-5000) linear array transducer with color and power Doppler capability. The following US characteristics were evaluated: the type of vascularization on the color or power Doppler US, echogenicity, outline, the ratio of the anteroposterior/transverse (AP/T) diameters, and the presence or absence of halo sign, cystic change, and microcalcifications.

The type of vascularization in all lesions was evaluated during the color or power Doppler US examination. Doppler amplification was controlled so that the normal thyroid tissue did not show any noise. Four types of vascularization were identified: type I, absence of flow signals; type II, presence of peripheral vascularization; type III, presence of peripheral and central vascularization; and type IV, presence of penetrating or central vascularization. Type IV vascularization was defined as one or more central or penetrating color signals without any peripheral circular vascularity.

The echogenicity of the nodule, which was assessed with respect to the normal parenchyma of the thyroid gland and strap muscle, was classified as markedly hypoechoic (more hypoechoic compared with the strap muscle), hypoechoic (more hypoechoic compared with the normal thyroid parenchyma, but more hyperechoic than the strap muscle), isoechoic (isoechoic compared with the normal thyroid parenchyma), hyperechoic (more hyperechoic than the normal thyroid parenchyma), or mixed (a nodule containing both hypo- and hyperechoic areas). The outline of the nodule was assessed with respect to the smoothness and definability of the nodule, and was classified as regular, irregular, or lobular. The halo sign was defined as an anechoic or hypoechoic peripheral rim surrounding the nodule. Microcalcifications were defined as tiny echogenic spots with or without the acoustic shadows.

Two radiologists (SKL and SW), who were blinded to the patients' diagnosis, interpreted the gray-scale and color or power Doppler US images. The final diagnosis was reached by consensus.

The relationship between the qualitative variables, i.e., type of vascularization on color or power Doppler US, echogenicity, outline, ratio of AP/T diameters, and presence or absence of halo sign, cystic change, and microcalcifications, and subtypes of PTC (classic type of PTC versus PMC) was assessed using a chi-square test.

The relationship between the same qualitative variable and the subtypes of PTC (classic type of PTC and PMC versus FVPTC) was assessed using a Fisher exact test.

Results

The long diameter of the lesions ranged from 10.4 mm to 60.4 mm (mean: 19.7 mm) for the classic type of PTC, from 2.0 mm to 10.0 mm (mean: 6.6 mm) for PMC, and from 4.1 mm to 54.5 mm (mean: 21.8 mm) for FVPTC. The most common type of vascularization on color or power Doppler US was type IV, I and II in the classic type (Fig. 1), PMC (Fig. 2), and FVPTC (Fig. 3), respectively (Table 1). With regard to vascularization of the lesions, type I was significantly more common in PMC (p

$<.0001$) than in the other two subtypes, type III in FVPTC ($p<.000001$), and type IV in classic type of PTC ($p=.0001$). Table 2 shows the echogenicity of the individual subtypes of PTC. The echogenicity was most commonly hypoechoic in the classic type and PMC (Figs. 1, 2), and isoechoic in FVPTC (Fig. 3) (Table 2).

Table 1. Types of Vascularization of the Subtypes of PTC

	Classic Type ($n=69$)	PMC ($n=67$)	FVPTC ($n=23$)
Type I	15 (21.7%)	38 (56.7%)*	2 (8.7%)
Type II	-	-	2 (8.7%)
Type III	2 (2.9%)	2 (3.0%)	19 (82.6%)*
Type IV	52 (75.4%)*	27 (40.3%) [†]	-

*Significantly frequent than other two subtypes

[†] Significantly frequent than one of other subtypes

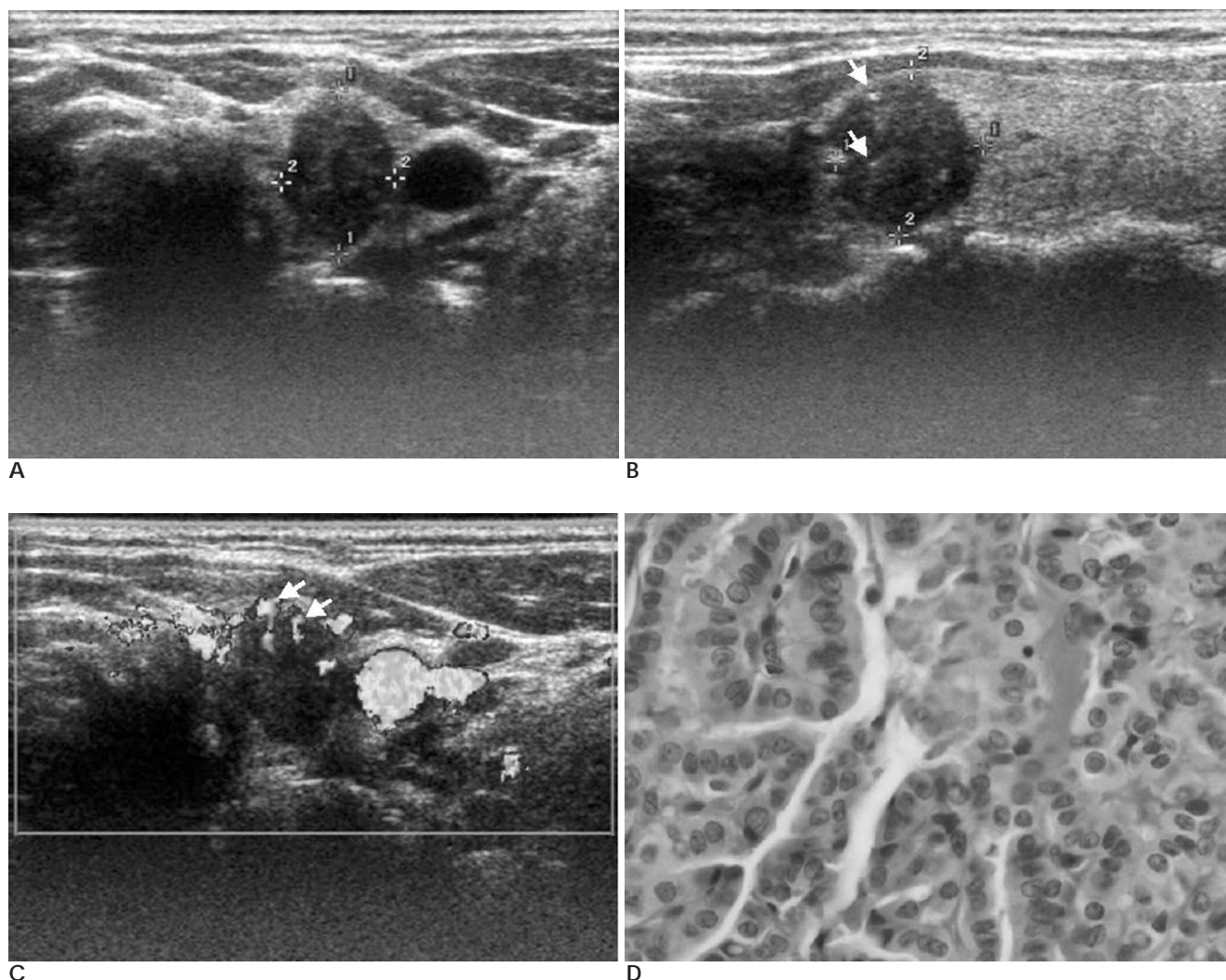


Fig. 1. A 44-year-old woman with the classic type of papillary thyroid carcinoma (PTC)

Transverse (A) and longitudinal (B) gray-scale ultrasonographic (US) images show an irregular hypoechoic solid mass (delineated by electronic calipers), more elliptical in shape, with microcalcifications (arrows) in the left thyroid lobe. Transverse color Doppler US image (C) demonstrates penetrating vessels (arrows) within the mass. Histologically (D), the tumor cells show markedly pleomorphic nuclei with a ground-glass appearance, intranuclear pseudoinclusions and grooves (H & E, $\times 600$).

With regard to the echogenicity of the nodules, hypoechogenicity was more frequent in PMC than in the other two subtypes ($p < .003$), and iso- ($p < .000034$) and hyperechogenicity ($p < .0151$) was more common in FVPTC. The outline was most frequently irregular in the classic type and PMC (Figs. 1, 2), and regular in FVPTC (Fig. 3) (Table 3). With respect to the outline of

Table 2. Echogenicity of the Subtypes of PTC

	Classic Type (<i>n</i> = 69)	PMC (<i>n</i> = 67)	FVPTC (<i>n</i> = 23)
Markedly hypoechoic	33 (47.8%)	50 (74.6%)*	6 (26.1%)
Hypoechoic	25 (36.2%) [†]	6 (26.1%)	6 (26.1%)
Isoechoic	-	7 (30.4%)*	7 (30.4%)*
Hyperchoic	-	3 (13.0%)*	3 (13.0%)*
Mixed	11 (16.0%)	-	1 (4.4%)
Calcifications only	-	1 (1.5%)	-
		3 (4.5%)	

*Significantly frequent than other two subtypes

[†]Significantly frequent than one of other subtypes

the lesions, PMC was more frequently irregular than in the classic type of PTC ($p = 0.0014$) or FVPTC ($p < .000001$), and FVPTC was more often regular than either the classic type or PMC ($p < .000001$). The ratio of the AP/T diameters was 1.0 or more in 22/69 (31.9%) of the classic type (Fig. 1), 37/67 (55.2%) of the PMC (Fig. 2), and 3/23 (13.0%) of the FVPTC. Halo sign was present in 21/69 (30.4%) of the classic type, 4/67 (6.0%) of the PMC, and 18/23 (78.3%) of the FVPTC (Fig. 3). Cystic changes were noted in 1/69 (1.4%), 0%, and 5/23 (21.7%) of the classic type, PMC, and FVPTC (Fig. 3), re-

Table 3. Outline of the Subtypes of PTC

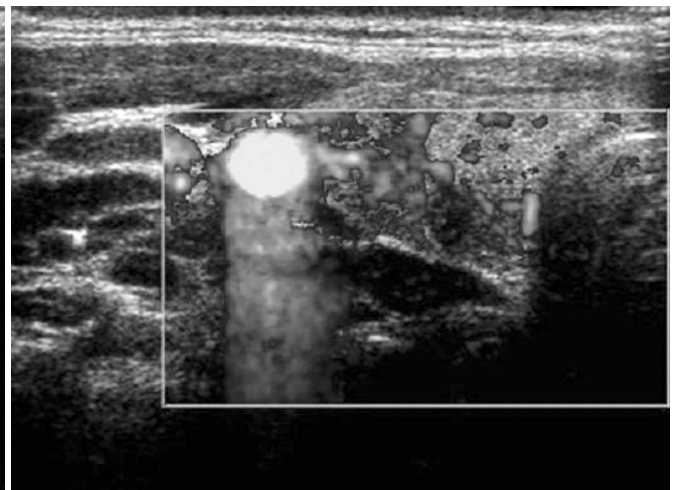
	Classic Type (<i>n</i> = 69)	PMC (<i>n</i> = 67)	FVPTC (<i>n</i> = 23)
Irregular	42 (60.9%) [†]	58 (86.6%)*	-
Regular	10 (14.5%)	8 (11.9%)	21 (91.3%)*
Lobular	17 (24.6%)	2 (8.7%)	

*Significantly frequent than other two subtypes

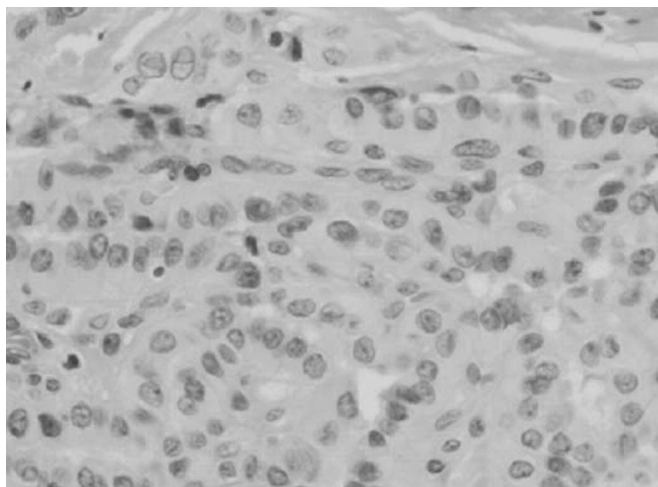
[†]Significantly frequent than one of other subtypes



A



B



C

Fig. 2. A 38-year-old woman with classic type of papillary microcarcinoma (PMC)

Transverse gray-scale ultrasonographic (US) image (A) reveals an irregular markedly hypoechoic solid nodule (delineated by electronic calipers), more elliptical in shape, in the right thyroid lobe. Transverse power Doppler US image (B) shows no color signals within the nodule. Histologically (C), the tumor cells demonstrate prominent pleomorphism with ground-glass appearing nuclei, and intranuclear pseudoinclusions and grooves (H & E, × 600)

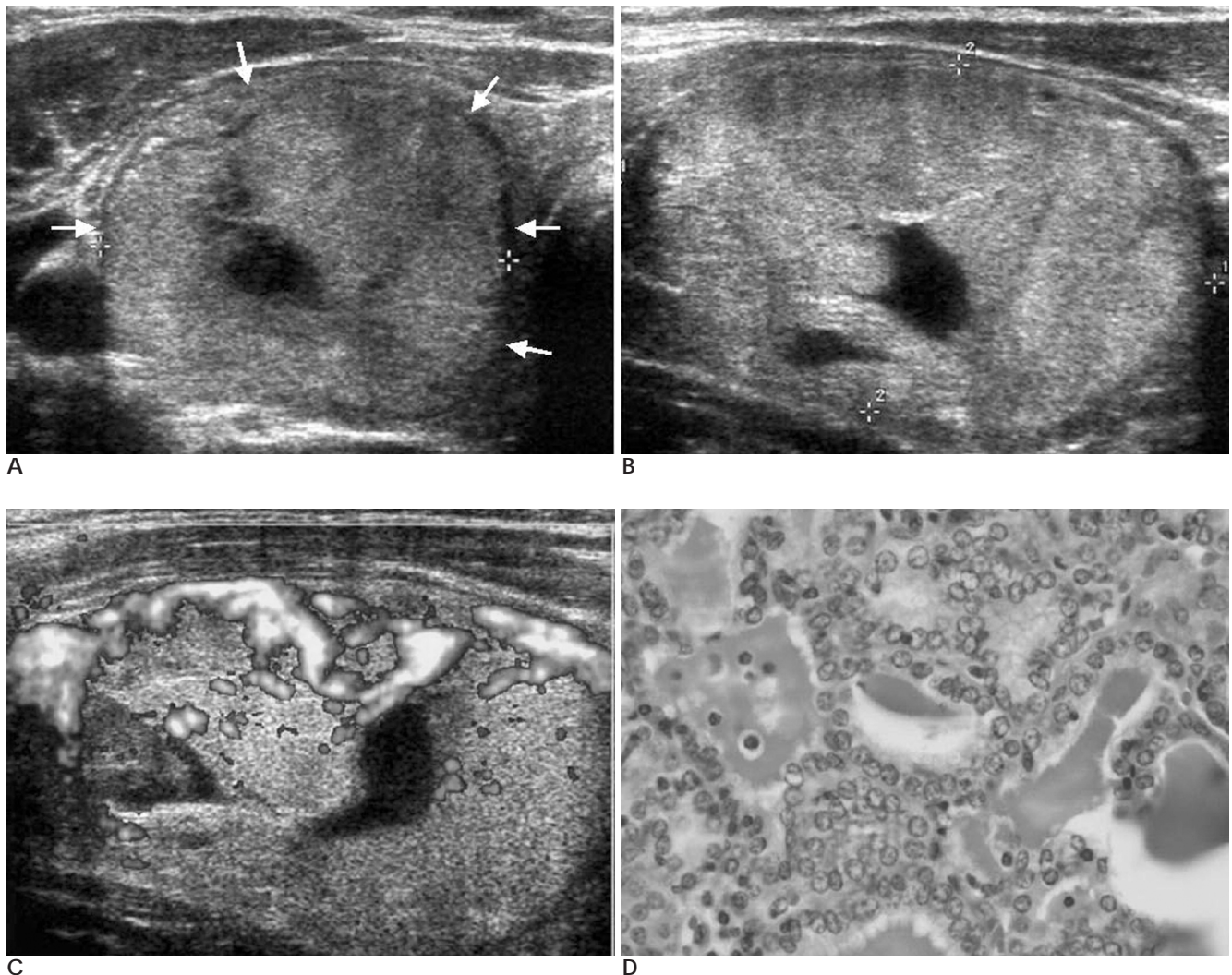


Fig. 3. A 53-year-old man with follicular variant of papillary thyroid carcinoma (FVPTC) Transverse (A) and Longitudinal (B) gray-scale ultrasonographic (US) images show a large well demarcated isoechoic solid mass (delineated by electronic calipers) with cystic changes and a peripheral sonolucent halo (arrows in A) in the right thyroid lobe. Longitudinal power Doppler US image (C) reveals peripheral and central color signals. Microscopic finding (D) of tumor mass demonstrates atypical follicular cells forming follicles. The nuclei of the tumor cells shows a ground-glass appearance with intranuclear pseudoinclusions and grooves (H & E, $\times 400$).

spectively. Microcalcifications were present in 38/69 (55.1%) of the classic type (Fig. 1), 19/67 (28.4%) of the PMC, and 3/23 (13.0%) of the FVPTC. A lesion was more elliptical in shape was identified more frequently in the PMC than in the classic type ($p = .0101$) or FVPTC ($p = .000505$). Halo signs were found more often in FVPTC than in the classic type ($p = .000078$) or PMC ($p < .000001$), and more frequently in the classic type than in PMC ($p = .0005$). Cystic changes were more common in FVPTC than in the classic type ($p = .003398$) or PMC ($p = .000766$), and there were more microcalcifications in the classic type than in PMC ($p = 0.0029$) or FVPTC ($p = .000522$).

Discussion

Papillary thyroid carcinoma is the most common histological type of thyroid cancer, accounting for 85% of cases (10, 11). Interestingly, the overall incidence of PTC has increased over the past several decades. With the increasing use of high-resolution US and fine-needle aspiration cytology (FNAC), thyroid nodules that are too small to be palpated are being discovered more often (12). The classic type of PTC is the most common form of PTC. According to the World Health Organization (WHO), a papillary microcarcinoma is defined as a small PTC with the maximal diameter measuring 10

mm or less (9). An autopsy series showed that papillary microcarcinomas have a prevalence ranging from 5.6% to 35.6% depending on the meticulousness of the examination and the diagnostic criteria (13 - 15). Although most patients with PMC have a benign clinical course, PMC with an invasive course has also been demonstrated (16). The FVPTC is the second most common subtype of PTC after classic PTC, accounting for 10% to 15% of all cases (17). It is defined by a follicular architecture with the nuclear features of classic PTC. Although it has been suggested that FVPTC may behave differently from a normal papillary thyroid carcinoma (18), a large series has shown that the pattern of behavior of FVPTC and the usual papillary carcinoma are similar, except for a tendency toward more extracervical metastases in FVPTC (19).

The primary goal of US in an evaluation of focal thyroid lesion was to determine which thyroid lesions are malignant and therefore warrant FNA (20). Several US characteristics have been examined as potential predictors of a thyroid malignancy, including the presence of microcalcifications, an irregular outline, marked hypoechogenicity, the absence of halo signs, a more elliptical shape, increased intranodular vascularization, and a predominantly solid composition (2 - 4, 21). However, as already reported by Chan *et al.* (2), there is a broad spectrum of sonographic findings in PTC. Half of the PTC in their series had at least one uncommon sonographic feature.

In this study, the PMC was regarded as a separate entity from the classic type of PTC in determining if there were any differences between gray-scale and color or power Doppler US features according to the size of the classic type of PTC. Interestingly, with regard to the type of vascularization, echogenicity, outline, ratio of the AP/T diameters, the presence of halo signs and microcalcifications, there were statistically significant differences between the classic type of PTC and PMC, *i.e.*, PMC was more often avascular, hypoechoic, and more likely to have an irregular outline than the classic type. In contrast, the halo sign and microcalcifications were found more commonly in the classic type of PTC. These results were somewhat unexpected, and similar results have not been reported in the English literature.

The role of color or power Doppler US in evaluating thyroid nodules for a malignancy is unclear. Recently, Lebrowska *et al.* (22) examined thyroid nodules using power Doppler US and an immunohistochemical reaction. The increased flow pattern in the center nodules

on power Doppler US correlated with the proliferative activity, and consequently with a malignancy. Holden (23) observed different types of vascularization in benign nodules and carcinomas, in that the carcinomas had a greater degree of internal vascularization. In contrast, Shimamoto *et al.* (24) reported that there was no correlation between the extent and type of vascularization and the nature of the nodules. Vascular endothelial growth factor (VEGF) is present in the epithelial cells of normal thyroid gland, Graves' disease, thyroiditis, and thyroid tumors. Increased VEGF is demonstrable in thyroid cancers in contrast to the normal gland or benign tumors (25). Similarly, the microvascular density of the tumors is higher in malignant tumors than in benign tumors (26). There is a good correlation between the circulating VEGF levels and the intrathyroidal vascular area assessed by color flow Doppler ultrasonography (27). Interestingly, a papillary microcarcinoma does not show higher VEGF expression than the normal thyroid gland (25). This may indicate an absence of color signals in many cases (56.7%) of PMC and in some cases (21.7%) of the classic type of PTC. All the cases with the classic type of PTC that did not show color signals in the center of the nodule were < 15 mm in the long diameter. The frequent type IV vascularization of the classic type of PTC and PMC might be due to the frequent absence of complete encapsulation. Moreover, the common type III vascularization in FVPTC may be related to the common encapsulation in this type of PTC (28).

Although there are certain trends in the US observations of benign and malignant thyroid nodules, there is also some overlap in their appearance (2, 29). This may result when attempting to distinguish between benign and malignant lesions according to the above-mentioned criteria without considering the histological types of thyroid carcinoma. Therefore, before attempting to distinguish between benign and malignant lesions it is appropriate to classify the thyroid tumor into two growth patterns, *i.e.*, papillary and follicular. This is because many follicular neoplasms, *i.e.*, follicular adenoma, follicular carcinoma, and FVPTC, may be categorized as benign lesion when using above-mentioned US characteristics even though they are malignant. Hence, different diagnostic criteria should be applied for lesions suggestive of follicular neoplasms to distinguish between benign and malignant follicular lesions. Neither conventional US nor FNA yielded satisfactory results in the differentiation of benign and malignant follicular neoplasms of the thyroid (6). Some authors suggested that the vascular

pattern and velocimetric parameters might be useful (30) but there is some controversy (24).

The US findings of the subtypes of papillary carcinoma also may differ significantly. However, to the best of our knowledge, there are no reports comparing the features of gray-scale with those of color or power Doppler US corresponding to the individual subtype of PTC. This study applied these US criteria of a thyroid malignancy to the individual histological subtype of PTC and found that FVPTC had many of the US features of benign tumors: (1) peripheral and central vascularization (82.6%), (2) isoechoic internal echogenicity (30.4%), (3) regular (91.3%) or lobular (8.7%) outline, (4) ratio of AP/T diameters less than 1 (87%), (5) frequently documented halo sign (78.3%), (6) frequent cystic change (21.7%), and (7) less frequent microcalcifications (13%) compared with the other two subtypes. There are few reports of the US findings of FVPTC (8). Komatsu et al. (8) retrospectively examined the preoperative US diagnosis of six patients with FVPTC. According to their study, only one of the six cases was preoperatively diagnosed with a papillary carcinoma, the remainder were diagnosed with a follicular adenoma (four patients), and an adenomatous goiter (one case). It is believed that FVPTC significantly contributes to the overlap between benign and malignant US features. Therefore, in order to avoid a misdiagnosis, it is important to determine if the mass has a papillary or follicular growth pattern before attempting to evaluate the PTC.

In conclusion, there is a significant difference between the gray-scale and color Doppler US features corresponding to the histological subtypes of PTC. The US features of FVPTC are significantly different from the other subtypes in that they tend to have more benign US characteristics than those of the classic type or PMC.

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: 가 classic type (75.4%) , PMC (56.7%) , FVPTC (82.6%) classic type PMC 가 47.8% 74.6% 가 , FVPTC (30.4%)가 가 classic type PMC 가 60.9% 86.6% 가 , FVPTC (91.3%)가 가 . * / 가 1.0 , classic type 31.9%, 30.4%, 1.4% 55.1% , PMC 55.2%, 6.0%, 0% 28.4% , FVPTC 13.0%, 78.3%, 21.7% 13.0%

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