Diagnosis of Thyroid Follicular Carcinoma by the Vascular Pattern and Velocimetric Parameters Using High Resolution Pulsed and Power Doppler Ultrasonography

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Abstract. The aim of this study was to define the preoperative diagnosis of thyroid follicular carcinoma by the vascular pattern and velocimetric parameters using high resolution pulsed and power Doppler ultrasonography (US). We compared the vascular pattern and the velocimetric parameters, such as peak systolic velocity (Vmax), end-diastolic velocity (Vmin), pulsatility index (PI), or resistance index (RI) between follicular adenoma (FA, n = 25) and follicular carcinoma (FC, n = 10) and analysed them by means of receiver characteristics curves (ROC). Of 10 patients with FC, 8 (80%) patients presented a moderate increase of intranodular vascularization using power Doppler US. In contrast, the majority (84%, 21 out of 25 cases) of FA cases showed only a peripheral rim of color flow even by power Doppler US. These color flow imagings by power Doppler US were suggested to be a reliable tool for the differential diagnosis of thyroid follicular tumor with a sensitivity of 87.5% and a specificity of 92%. In velocimetric analyses, the Vmax/Vmin ratios, PI, and RI were significantly higher in the patients with FC than those with FA (p<0.001, p<0.005, and p<0.001, respectively). By means of ROC, FC could be diagnosed with a cutoff value of ratio of PI (>1.35), RI (>0.78), and Vmax/Vmin (>3.79). The diagnostic efficiency evaluated by ROC curves were 0.898 for PI, 0.876 for RI, and 0.888 for Vmax/Vmin, respectively. In conclusion, the evaluation of the vascular pattern and the velocimetric parameters using pulsed and power Doppler ultrasound may provide important information that is useful in making correct differential diagnosis of malignant or benign thyroid follicular tumor preoperatively.

Key words: Thyroid ultrasonography, Power Doppler ultrasonography, Follicular carcinoma, ROC curve

A series of diagnostic modalities including ultrasonography (US), scintigraphy, and fine-needle aspiration biopsy (FNAB) currently are employed before treatment of thyroid neoplasms. Papillary carcinoma, the most common type of thyroid carcinoma, can be diagnosed by the characteristic ultrasonographic findings of irregular shaped hypoechogenic nodule, and intranodular microcalcification with over 90% sensitivity and specificity [1–4]. In contrast, follicular carcinoma is only defined by the presence of capsular or vascular invasion histopathologically, and it is still impossible to differentiate the minimal invasive type of follicular carcinoma from benign follicular adenoma. Extensive angioinvasion, local invasion, or distant metastases in older patients with follicular carcinoma appears to be strong independent predictors of poor outcome [5]. In general, a characteristic gray-scale US findings suggestive of follicular carcinoma (FC) are: solitary and solid hypoechogenic tumor with inhomogeneous internal texture, irregular ill-defined margin, and absent or discontinuous peripheral sonolucent echo [6, 7]. An increasing tumor size over a short period is often observed in FC and intranodular cystic degeneration is frequently observed in FA, but is rare in FC. However,
these gray-scale US findings may be typical and easily diagnosed in widely invasive type FC, but is quite difficult for differential diagnosis of the minimally invasive type FC and FA. Recently, high resolution pulsed and color Doppler US (CD) are widely used as non-invasive procedures that can easily obtain interesting data about the vascularity of parenchymatous structures. Recent investigators have indicated that the contemporary means of evaluating morphology and vascular structures may have an important role in the differential diagnosis of benign and malignant tumor [8–14]. But, to date, the application of power Doppler US to thyroid follicular tumor analysis has not been demonstrated as having definite clinical usefulness.

To determine whether high resolution pulsed and color Doppler US would be useful in the differential diagnosis between follicular adenoma and follicular carcinoma, the vascular patterns were evaluated using power Doppler sonography and the receiver operating characteristic (ROC) analysis was performed on velocimetric parameters to evaluate the diagnostic efficiency of the criteria on the basis of the area under the ROC curve.

**Patients and Methods**

**Patients**

Of the 35 patients in this study who underwent surgery, 10 patients were diagnosed in follicular carcinoma, and 25 patients in follicular adenoma. The functioning adenoma, called Plummer disease and recognized “hot nodule” in scintigraphy, were excluded in this study. Histologically, follicular carcinomas were classified as minimally invasive type (n = 6) and widely invasive type (n = 4). One patient with minimally invasive type and three out of 4 cases with widely invasive type were observed to have distant metastases of lung and bone. All these patients with a mean age of 45.3 years, (range, 18–83 years: 11 males, 24 females) were preoperatively investigated with high resolution pulsed and color Doppler US to evaluate the morphologic and vascular features of tumor. In ROC analysis, the data were also compared between benign and malignant tumor including 18 cases with adenomatous nodules and 30 cases with papillary carcinoma. Informed consent was obtained from patients before the US evaluation.

**US evaluation**

The US study was performed using an electronically focused 7.5 MHz linear transducer (GE Yokogawa Medical Co., Japan). The lower resolution for the detection of flow velocity was 3 cm/second. The diameter of long-axis, short-axis, and the depth was estimated and the volume (cm$^3$) of each tumor was calculated using the approximate formula of the ellipsoid $\pi/6 \times (length) \times (width) \times (depth)$. The pattern of vascularization in the tumor was evaluated by power Doppler US, and was categorized to define a vascularization score (VS) as follows: 1 = no vascularity, 2 = peripheral vascularization, 3 = intranodular vascularization, 4 = abundant intranodular and peripheral vascularization. In cases of abundant blood flow inside the tumor, the most vigorous flow detected by power Doppler US was selected in the velocimetric analyses. The angle-independent velocimetric indexes, pulsatility index (PI), and resistance index (RI) were measured using on-board software as follows: $PI = (peak \ hypothelial \ velocity \ minus \ end \ diastolic \ velocity)/time-averaged \ maximum \ velocity$. $RI = (peak \ systolic \ velocity \ minus \ end \ diastolic \ velocity)/peak \ systolic \ velocity$.

**Statistical analysis**

The numbers of true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) US diagnoses were determined. Sensitivity was calculated as $TP/(TP + FN)$, and specificity was calculated as $TN/(TN + FP)$. The statistical analysis was performed using SAS statistical software for Macintosh (SAS Institute Inc., Cary, NC). *P*<0.05 was considered statistically significant. Quantitative data are presented as mean values and standard deviations (SD), and the differences in parameter values between benign and malignant tumor were analyzed with the nonparametric Mann-Whitney U test. The Fisher exact probability test and the chi-square test were used to evaluate the differences in the distribution of ordinal and categorized parameters between the two groups. The Spearman rho correlation coefficient was calculated for correlation analysis. A stepwise logistic regression was performed to select the variables that independently and significantly contributed to the classification of benign and malignant thyroid nodules. The receiver operating characteristic (ROC) analysis was subsequently performed on these variables to evaluate the overall
diagnostic efficiency of the criteria on the basis of the area under the ROC curve.

**Results**

Thirty-five patients were enrolled in this study and subjected to histopathological evaluation which included 25 cases of follicular adenoma (FA) and 10 cases of follicular carcinoma (FC). As shown in Fig. 1, power Doppler US, which shows the degree of Doppler power and is possible to represent the lower velocity vessels, revealed the more detail vascular structure compared to those with velocity-mode color Doppler US in patients with follicular carcinoma. Of 10 patients with follicular carcinoma, 8 patients (80%) presented internal hypervascularization using power Doppler US with a mean vascularization score of 3.6 ± 0.5. In contrast, the majority (84%) of the FA cases showed the peripheral vascular pattern, and only four cases (16%) of FA with a large tumor size of 3.2 ± 1.2 cm showed the increased intranodular vascularization with power Doppler US. The mean vascularization score in all FA cases was 2.4 ± 0.7, which was significantly lower vascularity compared to those of FC (P = 0.015). There was no significant relationship between the tumor size and the degree of vascularization in any of the groups. These results suggest that the evaluation of intranodular vascularization with power Doppler US is useful to diagnose of follicular carcinoma with a sensitivity of 80% and a specificity of 84%.

The descriptive analysis of the evaluated parameters and the statistical evaluation are presented in Table 1. Age, tumor size and tumor volume were matched in

![Fig. 1](image)

**Fig. 1.** B-mode (A) and Color Doppler sonogram in follicular carcinoma. Color flow mapping depicts more detailed construction of intranodular vessels in power-mode sonogram (C) compared to those in velocity-mode sonogram (B).

**Table 1.** Velocimetric analyses in benign and malignant follicular tumors

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>age (years)</th>
<th>tumor size (cm)</th>
<th>tumor volume (cm³)</th>
<th>Vmax (cm/sec)</th>
<th>Vmin (cm/sec)</th>
<th>Vmax/Vmin</th>
<th>Vmean (cm/sec)</th>
<th>PI</th>
<th>RI</th>
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<tbody>
<tr>
<td>FA</td>
<td>25</td>
<td>52 ± 14</td>
<td>3.4 ± 1.8</td>
<td>14.9 ± 17.8</td>
<td>24.7 ± 16.5</td>
<td>10.5 ± 9.4</td>
<td>2.7 ± 0.9</td>
<td>16.8 ± 13.5</td>
<td>0.9 ± 0.5</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>FCa</td>
<td>10</td>
<td>57 ± 14</td>
<td>3.5 ± 1.5</td>
<td>15.7 ± 16.4</td>
<td>41.3 ± 18.5*</td>
<td>9.6 ± 5.6</td>
<td>5.1 ± 2.5***</td>
<td>22.4 ± 13.2</td>
<td>1.7 ± 0.6**</td>
<td>0.8 ± 0.1*</td>
</tr>
</tbody>
</table>

FA: follicular adenoma, FCa: follicular carcinoma

*p<0.05, **p<0.005, ***p<0.001.

Data are shown as mean ± SD.
these two groups. The mean maximum peak velocity (Vmax) in FC was 41.3 ± 18.5 cm/sec, which was significantly higher than those of FA (24.7 ± 16.5 cm/sec, p<0.05). The end-diastolic velocity (Vmin) and mean velocity (Vmean) were not significant in the two groups. The ratio of Vmax/Vmin was the most significantly different parameter between the two groups (5.1 ± 2.5 in FC and 2.7 ± 0.9 in FA, p<0.001). PI and RI were also significantly higher in FC than in FA (1.7 ± 0.6 vs 0.9 ± 0.5 in PI, p<0.005 and 0.8 ± 0.1 vs 0.6 ± 0.2 in RI, p<0.05, respectively). There was no significant positive correlation between the tumor size or volume and these velocimetric parameters. When logistic regression analysis was performed, the vascular pattern and the parameters of pulse Doppler US were independently selected as significant parameters in predicting FC (data not shown).

To evaluate the diagnostic efficiency of the criteria on the basis of the area under the ROC curve, the ROC curves for PI, RI, and Vmax/Vmin ratios in follicular tumor are shown in Fig. 2A. The diagnostic efficiency calculated from the area under the ROC curve (AUC) were 0.898 for PI, 0.876 for RI, and 0.888 for Vmax/Vmin, respectively. From the ROC curve, the optimal cutoff points were calculated as 1.35 for PI, 0.78 for RI, and 3.79 for Vmax/Vmin, respectively. From this cut-point, the overall sensitivity and specificity were 90% and 89%, respectively. As shown in Fig. 2B, when compared between benign and malignant tumor including 18 cases with adenomatous nodules and 20 cases with papillary carcinoma, the cutoff points from ROC curves were calculated as 1.27 for PI, 0.73 for RI, and 3.74 for Vmax/Vmin, respectively.

**Discussion**

Although the majority of papillary carcinoma are easily diagnosed by ultrasonography and typical cytological findings of FNAB, preoperative discrimination between benign and malignant follicular tumor is still difficult. High resolution US is a first-step non-invasive diagnostic imaging technique used to evaluate the morphologic characteristics of thyroid nodules. In fact, in routine examination by B-mode US, follicular carcinoma has a tendency to show a hypoechoic solid tumor with inhomogeneous internal texture and the absence of the marginal sonolucent echo (halo sign) [6, 7]. Recently, color Doppler sonography is routinely done adjunct to routine sonography, so that more detail information about intranodular vascularization could be obtained. The use of pulsed and color Doppler US has
markedly improved the diagnostic accuracy in evaluating neoplastic tumor by identifying the vascular pattern in the tissues. In fact, the formation of abnormal new vessels has been reported to be associated with neoplastic growth [15], which it is rare in benign nodules. In particular, power Doppler sonography seems even more promising in the detection of low blood flow in small structures. It calculates the integrated strength of the Doppler signal, rather than the flow velocity and directional information, so it does not alias, is angle-independent, and is not substantially affected by noise [9, 13, 14]. Its increased flow sensitivity and better vascular delineation have been used to document the presence and characteristics of flow in vessels that are poorly imaged with conventional color Doppler. Thus, in this study, the vascular patterns of FC evaluated by power Doppler sonography could be of value in differentiating malignant FC from benign FA. In agreement with previous studies [2, 6, 8, 11], the color flow pattern of benign nodules demonstrated a peripheral rim of color flow or no color flow. This appearance is likely related to compression of normal thyroid tissue due to growth of the adenoma or adenomatous tissues. None of the carcinomas imaged demonstrated this type of color pattern, and in contrast, neovascularization is characteristic in neoplastic tumors. Actually, the ability to detect a color flow pattern within a small nodule depends on the transducer and equipment used. However, newlydeveloped sonographic units equipped with a high-frequency transducer have greatly improved the ability to detect superficial low velocity signals. From these points, the presence of an irregular diffuse intranodular blood flow are the best indicators of malignancy, and power-mode Doppler sonography significantly improves imaging of perinodular and intranodular blood flow when compared with conventional color flow Doppler. Fukunari [6] have also reported that color Doppler US could be useful in the differential diagnosis of FA and FC, and that the intranodular hypervascularity was characteristic in FC with a sensitivity of over 90%. In papillary carcinoma, as the most frequent type of thyroid carcinoma, many investigators [11, 16] have also reported that the prevalence of malignancy was greater when the nodule was hypervascular among solid nodules, and hypervascular cervical lymph nodes with a large ratio of largest to smallest diameter was suspicious to the metastases of thyroid cancer [17].

versely, Shimamoto et al. [18] did not find a correlation between the presence of specific color signals and pathology, as the detection of color signals was dependent on the size of the nodule rather than on its histology. Papini et al. [19] reviewed that irregular margins, intranodular vascular spots, and microcalcifications were independent risk factors of malignancy, and intranodular blood flow on color flow Doppler was reported in 66.6% of carcinoma and in 51.3% of benign nodules, concluding that the predictive value of CFD alone was poor. Although these reports insist that color Doppler imaging is not useful in the differential diagnosis of benign and malignant tumors and that it plays only a limited role in the evaluation of hormonal function such as cold or hot nodules [20], our study proposed that power Doppler imaging could play a more important role in the diagnosis of follicular carcinoma than the conventional B-mode or color-Doppler mode ultrasound or aspiration cytology.

Among the morphologic parameters evaluated in our group of patients, the vascularity parameters such as Vmax/Vmin, PI, and RI were significantly higher in follicular carcinoma, which improve the predictive value of US in differentiating benign from malignant thyroid nodules. In keeping with the results of other investigations, our data indicate that the contemporary, real-time evaluation of velocimetric parameters may provide more information for the correct classification of follicular tumor. In fact, the ROC analysis indicates that the cutoff value should be modified in relation to vascularity if the best diagnostic efficacy is to be achieved. By ROC analyses it was demonstrated for the first time that follicular carcinoma could be diagnosed at the point of intranodular hypervascularity with a high pulsatility index (PI>1.35), a high resistivity index (RI>0.78), and a high ratio of peak systolic velocity/end-diastolic velocity (Vmax/Vmin>3.79).

In conclusion, our data suggest that follicular tumor with hypervascularity and the increased ratio of Vmax/Vmin, PI, or RI could be diagnosed as follicular carcinoma more precisely. Even if no correspondence was found between the different aspects of blood flow and the histologic types of lesions, the vascular pattern by power Doppler US could be additionally helpful to diagnosis as follicular carcinoma, and it seems to be more sensitive and reliable than velocity-mode color Doppler US in the screening of thyroid nodules. In this study, the cases of follicular carcinoma are too limited to evaluate the significance between benign and malignant thyroid nodules. A study of larger populations is desirable to state the conclusions.
References