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CLINICAL EVALUATION OF COLOR-DOPPLER IMAGING FOR THE DIFFERENTIAL DIAGNOSIS OF THYROID FOLLICULAR LESIONS

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Abstract

Objects. Ultrasonography of the thyroid gland has recently proved to be a useful clinical diagnostic method, and the newly developed high-resolution ultrasonography with color-Doppler flow mapping function can reveal fine details of the thyroid gland and the hemodynamic features of thyroid neoplasmas. Ultrasonography can yield a diagnostic accuracy of over 90% in thyroid carcinoma, especially papillary carcinoma. However, neither conventional B-mode ultrasound imaging nor aspiration biopsy cytology has delivered satisfactory results for follicular carcinoma. The aim of this study was to evaluate the clinical usefulness of color-Doppler imaging for the differential diagnosis of thyroid follicular lesions

Subjects and Methods. A color-Doppler was performed in 310 patients with a solitary cold nodule, and a combination of B-mode US and color-Doppler findings, including tumor vascularity and results of a FFT analysis were used to create the following diagnostic grading system for differential diagnosis of follicular lesions: Grade 1, benign follicular lesion (no color flow mapping (CFM) inside the nodule); Grade 2, benign peripheral type (CFM only in peripheral area, PI <1.0); Grade 3, suspected follicular carcinoma (penetrating CFM, vascularity moderate); Grade 4, follicular carcinoma (high-velocity penetrating CFM, PI **>** 1.0). All patients were subjected to surgical resection, and histological examination was used to confirm the diagnosis.

Results. The grades of the177 adenomatous nodules were: Grade 1, 46.9%; Grade 2, 48.0%; Grade 3, 5.1%; and Grade 4, 0%. The corresponding percentages for the 89 follicular adenomas were 16.9%, 49.4%, 30.3%, and 3.4%; and for the 44 follicular carcinomas, 0%, 13.6%, 45.5%, and 40.9%. On the assumption that Grade 1 and 2 lesions are benign and Grade 3 and 4 lesions are malignant, 38 of the 44 follicular carcinomas and 227 of the 266 benign tumors had been accurately diagnosed, yielding a sensitivity of 88.9%, a specificity of 74.2%, and an accuracy of 81.0% for the grading system.

Conclusion. Color-Doppler imaging examination of 310 follicular tumors has revealed that high-velocity pulsative blood flow penetrating the tumor is a characteristic finding of follicular carcinoma, and that yielded a new diagnostic criteria for color-Doppler imaging. The differential diagnostic grading scores for color-Doppler examinations and the results of FFT analysis can show a diagnostic usefulness. Ultrasound with the color-Doppler function can play an important role in the differential diagnosis of thyroid tumors.

Introduction

Use of high-frequency transducers with frequencies of 7-15 MHz allows detection of very small (2~3mm) thyroid tumors, and as a result, ultrasonography is the imaging modality of first choice for the diagnosis papillary tumors [1]. It may detect masses and metastatic lymph nodes that have not been identified by palpation, and very small papillary carcinomas, even in adenomatous goiters and cystic lesions, can be detected, and accuracy of diagnosis based on the characteristic echogenicity and calcification, was obtained over 90% during the past decade in Japan.[2, 3]. No significant ultrasound patterns, such as internal echo, calcification, or invasion findings, which are characteristic US findings in papillary carcinoma, are not useful for the differential diagnosis from follicular adenoma and carcinoma except the low degree of cystic degeneration [4] (Fig. 1). The results of the present study showed that follicular carcinoma could not be accurately diagnosed in 50%. Neither conventional ultrasound imaging nor aspiration biopsy cytology yields satisfactory results [5, 6] (Fig.2 and 3).

Microvascular envelopment of neoplastic tumor is considered to be watched with keen clinical interest, and color-Doppler (CD) examinations can play an initial and important role in the detection of the vascular structure and vascularity of tumors without contrast medium [7,8].

The aim of this study was to evaluate the clinical usefulness of CD imaging for the differential diagnosis of thyroid follicular lesions .

Patients and methods

CD examination was performed in 310 patients (266 females and 44 males, age range: 11-84 yr, median: 47 yr) with a solitary cold nodule in the thyroid gland. All patients underwent surgical resection, and histological examination was used to confirm the diagnosis. The average diameter of the tumors in this study was 45.3 ±19.8 mm (mean±SD), and no statistically significant differences in size were found between the histological classifications (Fig. 4). Cases with papillary carcinoma, Graves' disease, Hashimoto's thyroiditis, and autonomous functioning tumors were excluded from this study. Both B-mode US and CD findings, including tumor vascularity and blood flow analysis, were used to create the following diagnostic grading system for the differential diagnosis of follicular lesions (Table 1) (Fig. 5):

Grade 1: benign follicular lesion (no color flow mapping (CFM) inside the nodule

Grade 2: benign peripheral type (CFM only in peripheral area)

Grade 3: suspected follicular carcinoma (penetrating CFM, vascularity moderate)

Grade 4: follicular carcinoma (high-velocity penetrating CFM, PI>1.0)

Results

The final histological diagnosis of the surgical specimens in all 310 cases was adenomatous nodule in 177 cases, follicular adenoma in 89 cases, and follicular cancer in 44 cases. On the basis of the CD examination tumor vascularity was classified as: none, poor, moderate, and rich. In the 177 adenomatous nodules; tumor vascularity was none in 26 (14.7%), poor in 87 (49.1%), moderate in 50 (28.3%), and rich in 14 (7.9%). In the 89 follicular adenomas, tumor vascularity was none in 4(4.5%), poor in 20(22.5%), moderate in 50(56.2%), and rich in 15(16.8%), and in the 44 follicular carcinomas, it was none in 1 (2.3%), poor in 5 (11.4%), moderate in 25(56.8%), and rich in 13(29.5%) (Fig.6).

Blood flow analysis of minimum velocity and the PI index showed the statistical differences between adenomatous nodules, follicular adenoma, and follicular cancer ($p<0.0001$); but analysis of maximum velocity did not show any statistically differences (Figs. 7 and 8).

The receiver operating characteristics (R.O.C) of the PI index of the patients with follicular neoplasms yielded a satisfactory cutoff value of 1.01, a specificity of 79.0%, and sensitivity of 69.1%(Fig. 9). The ROC also had an area

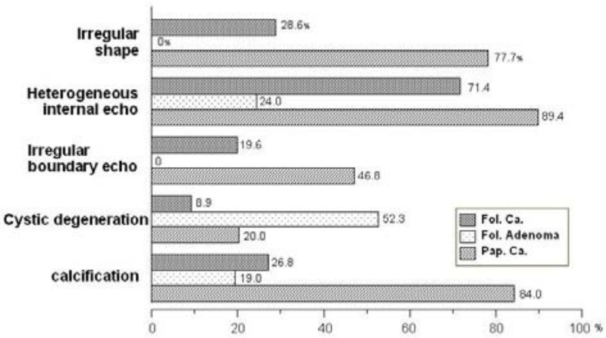

Fig.1. Characteristic US findings of thyroid tumors

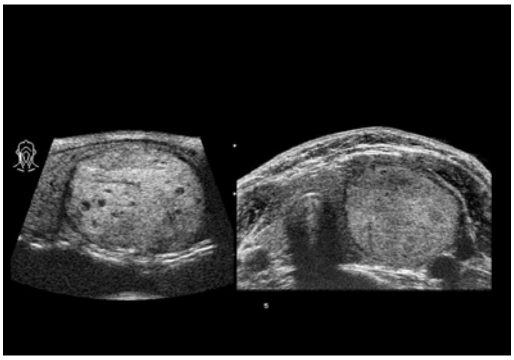

Fig.3. Ultrasonograms of thyroid follicular carcinoma (undetectable cases)
(Lt.) Oval shaped solid mass lesion with spotty cystic degeneration surrounded by a rim of low echoes (halo sign) in the right lobe of the thyroid.
(Rt.) Round mass with homogenous internal echogenicity and regular halo sign in the left lobe of the thyroid.
Both the US and the preoperative clinical diagnosis in these cases was a benign adenomatous nodule.

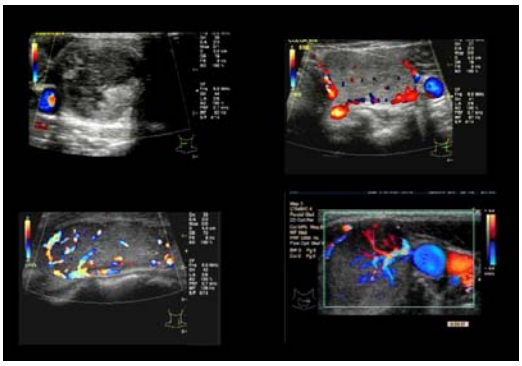

Fig.5. Characteristic CD images of lesions with different grading scores
(top left) Grade 1: No color flow mapping (CFM) inside the nodule.
(top right) Grade 2: CFM is seen only in the peripheral area.
(bottom left) Grade 3: Blood flow penetrating into the tumor is visualized and vascularity was judged to be moderate.
(bottom right) Grade 4: Several sources of blood flow are seen penetrating the tumor, and vascularity was judged to be rich. Blood flow analysis revealed high-velocity flow and pulsating feeding vessels with a pulsatility index (P.I.) of over 1.0.

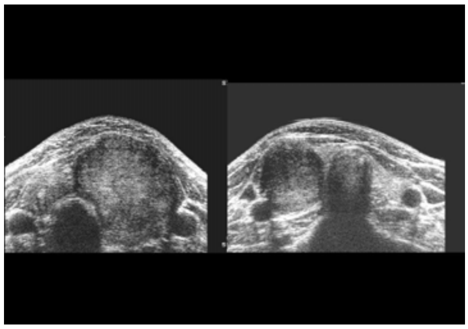

Fig.2. Ultrasonograms of thyroid follicular carcinoma (detectable cases)
(Lt.) irregularly shaped solid mass lesion with heterogeneous internal echo in left thyroid lobe
(Rt.) round tumor in the right thyroid lobe with low and irregular boundary echogenicity
No calcification or cystic degeneration was observed in these cases.

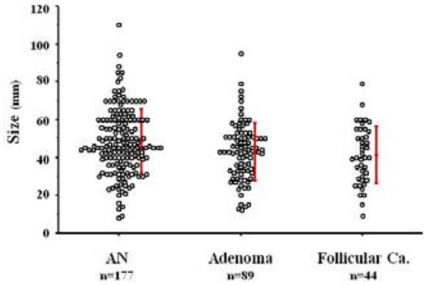

Fig.4. Differences in maximum tumor diameter according to histological classification.
No statistically significant differences were found between the cases with an adenomatous nodule, follicular adenoma, or follicular cancer in this series.

Fig.6. Tumor vascularity based on the results of the

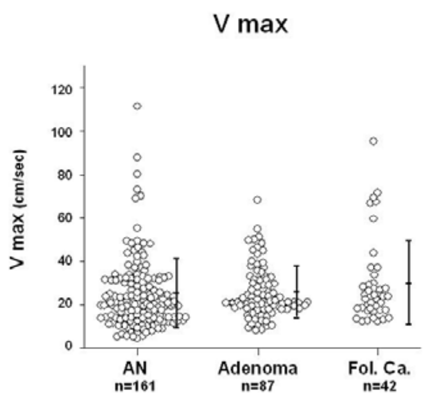

Fig.7. Blood flow analysis of V max (cm/sec)

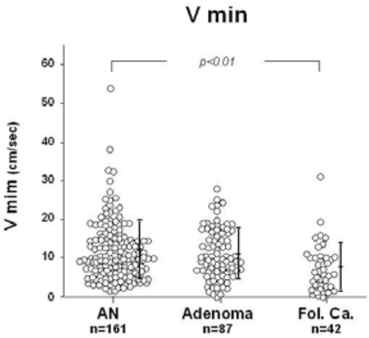

Fig.8. Blood flow analysis of V min (cm/sec)

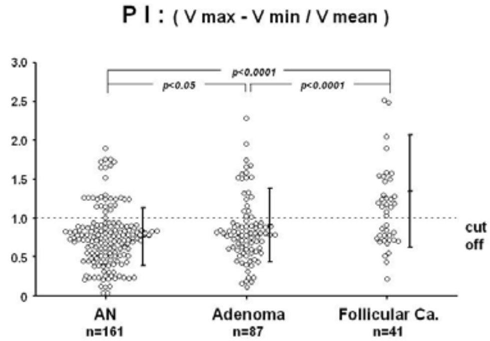

Fig.9. Differences in PI index between AN, adenoma, and follicular cancer. P I: (V max - V min / V mean)

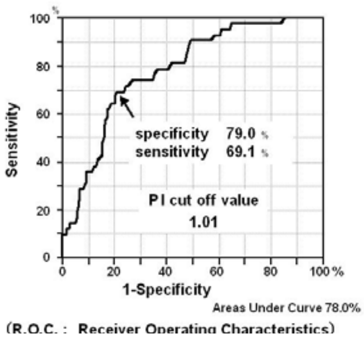

Fig.10. ROC. Curve of P I in patients with follicular neoplasms.

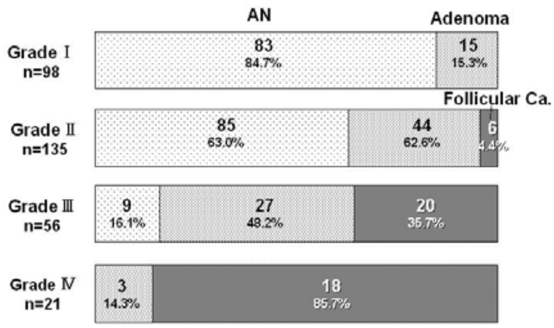

Fig.11. Results of differential diagnosis based on the grading score.

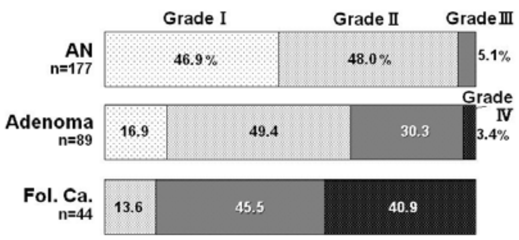

Fig.12: Results of differential diagnosis based on the histological type.

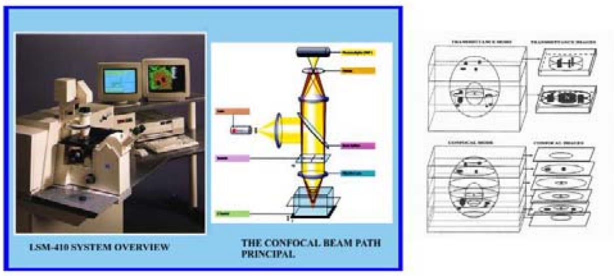

Fig.13. Structure and principle of the confocal laser scanning microscope.

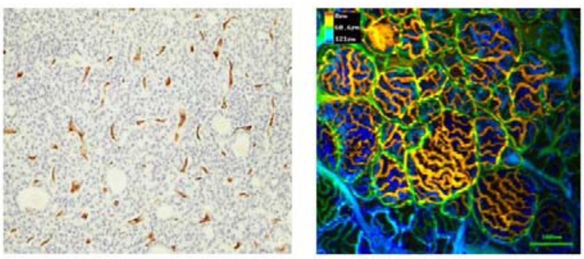

Fig.14. Histological appearance of thyroid follicular cancer and immunochemical staining for CD 34
(Lt.) Conventional microscopy

Table 1.
Criteria of the diagnostic grading system for the differential diagnosis of follicular lesions

	US B-mode	CD (Vascularity)	FFT* analysis
Grade 1	Benign	None	
Grade 2	Benign	Poor (Only the peripheral area)	PI<1.0
Grade 3	Follicular neoplastic	Poor~Moderate	PI<1.0
Grade 4	Follicular neoplastic	Moderate~Rich	PI>1.0

*FFT (Fast Fourier transformation): Blood flow with velocity and direction

under curve of 78.0% (Fig. 10).

The results of differential diagnosis by grading score in this study were as follows.

Of the 177 adenomatous nodules, 46.9% were Grade 1, 48.0%, Grade 2, 5.1% Grade 3, and 0% Grade 4. The corresponding percentage for the 89 follicular adenomas were 16.9%, 49.4%, 30.3%, and 3.4% and for the 44 follicular cancers, 0%, 13.6%, 45.5%, and 40.9% (Fig. 11). All 98 Grade 1 lesions were benign tumors, and consisted of 83 adenomatous nodules, and 15 follicular adenomas. The 135 Grade 2 lesions consisted of 85 adenomatous nodules, 44 follicular adenomas, and 6 follicular cancers. The 56 Grade 3 lesions consisted of 9 adenomatous nodules, 27 follicular adenomas, and 20 follicular cancers. The 21 Grade 4 lesions consisted of 3 follicular adenomas and 18 follicular cancers (Fig. 12). Assuming Grades 1 and 2 to be benign, and Grades 3 and 4 to be malignant, 34 of 44 follicular carcinomas and 227 of 266 benign tumors had been accurately diagnosed, yielding a sensitivity of 88.9%, a specificity of 74.2% and an accuracy of 81.0%.

Discussion

Neither conventional US nor FNA has yielded satisfactory diagnostic accuracy for thyroid follicular cancer. On the other hand, pathological management for thyroid follicular tumor is now controversial from several viewpoints, including the diagnosis of minimal capsular invasion and the difference between clinical course, outcome and histological diagnosis.

CD imaging of thyroid tumors is considered useful for observation of microvascular structure and vascularity, and it can play an initial and important role in differential diagnosis, especially in solid tumors without calcification [9, 10]. Some reports claim that CD imaging cannot rule out malignancy or play a role in differential diagnosis of thyroid cancer [11]. Our series consisted of 310 follicular tumors without papillary carcinoma and yielded different results from other reports, possibly because of exclusion of cases with sclerosing or calcified papillary carcinoma from our study. Papillary carcinoma is easy to be diagnosed by conventional US based on its characteristic calcification, irregular shape, and heterogeneous internal echogenicity. However, CD imaging cannot be used to obtain vascular images in sclerosing or calcified papillary carcinoma because of obstruction of Doppler signals. CD imaging of thyroid tumors is not useful for the diagnosis of papillary cancer, but it is clinically useful for the diagnosis of follicular cancer. Proper indications and use of CD examinations is considered to be required.

The tumor vascularity and the microenvironment of follicular lesions should be evaluated not only by the color Doppler method but by new histological approaches. Both US color Doppler, which can visualize hemodynamic features in real time, and confocal laser microscopy, which can reconstruct 3D vascular images, are expected to play an important role in making a new diagnostic criterion of follicular tumors. Laser scanning confocal microscopy, also referred to as confocal scanning laser microscopy, has now been established as a valuable tool for obtaining high-resolution images and 3-D reconstructions of a variety of biological specimens(Figs.13 and 14). In LSCM, a laser light beam is expanded to make optimal use of the optics in the objective. Through an x-y deflection mechanism the beam is converted into a scanning beam and focused on a small spot by an objective lens in a fluorescent specimen. LSCM allows the production of 3-D reconstructed images of the microvascular structure of thyroid tumors, that are very similar to CD images. The newly developed microscopic images enable confirmation of the characteristic microvascular structure of thyroid follicular cancer and may lead a new diagnostic criterion for the thyroid follicular cancer.

Conclusion

CD examination of 310 follicular tumors yielded high-velocity pulsative blood flow penetrating the tumor as a characteristic finding of follicular carcinoma.

A combination of the B-mode US and CD findings, including tumor vascularity and the results of blood flow analysis, have lead to the creation of a diagnostic grading system for differentiation of follicular lesions. The grading system provides useful criteria for the differential diagnosis of thyroid follicular cancer. The characteristic microvascular images obtained by CD imaging will be confirmed histologically by newly developed confocal scanning laser microscopy.

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