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Clinical Evaluation of Color Doppler Imaging for the Differential Diagnosis of Thyroid Follicular Lesions

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Abstract. Ultrasonography (US) of the thyroid gland has recently proved to be a useful clinical diagnostic method, and the newly developed high-resolution US with a color Doppler flow mapping function can reveal fine details of the thyroid gland and the hemodynamic features of a thyroid neoplasm. US can yield a diagnostic accuracy of more than 90% for thyroid carcinoma, especially papillary carcinoma. However, neither conventional B-mode US 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. A color Doppler scan 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 fast Fourier transform (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, pulsatility index (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 histologic examination was used to confirm the diagnosis. The grades of the177 adenomatous nodules were as follows: grade 1, 46.9%; grade 2, 48.0%; grade 3, 5.1%; 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 they were 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. Color Doppler imaging of 310 follicular tumors has revealed that high-velocity pulsatile blood flow penetrating the tumor is a characteristic finding of follicular carcinoma and is a new diagnostic criterion for performing color Doppler imaging. The differential diagnostic grading scores for color Doppler examinations and the results of FFT analysis demonstrate that US with the color Doppler function can play an important role in the differential diagnosis of thyroid tumors.

The use of high-frequency transducers with frequencies of 7 to 15 MHz allows detection of extremely small (2–3 mm) thyroid tumors.

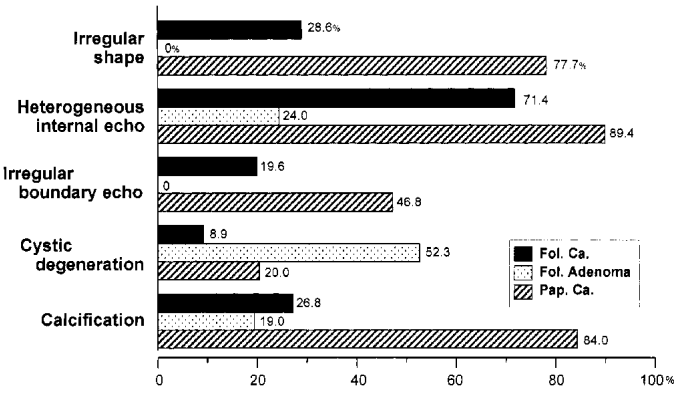

Fig. 1. Characteristic ultrasonographic (US) findings of thyroid tumors. Fol.: follicular; Pap: papillary; Ca: carcinoma.

As a result ultrasonography (US) is the imaging modality of choice for diagnosing papillary tumors [1]. US may detect masses and metastatic lymph nodes that have not been identified by palpation as well as extremely small papillary carcinomas, even in adenomatous goiters and cystic lesions. The accuracy of the diagnosis is based on characteristic echogenicity and calcification and was demonstrated to be higher than 90% during the past decade in Japan [2, 3]. No significant US patterns, such as internal echography, calcification, or findings of invasion, which are characteristic US findings for papillary carcinoma, are useful for a differential diagnosis that includes follicular adenoma and carcinoma, except the low degree of cystic degeneration [4] (Fig. 1). The results of the present study showed that follicular carcinomas are not accurately diagnosed in 50% of cases. Neither conventional US imaging nor aspiration biopsy cytology yield satisfactory results [5, 6] (Figs. 2, 3).

The microvascular envelopment of a neoplastic tumor may be a differentiating feature of significant clinical interest, and color Doppler (CD) examinations can play an initial and important role in detecting 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.

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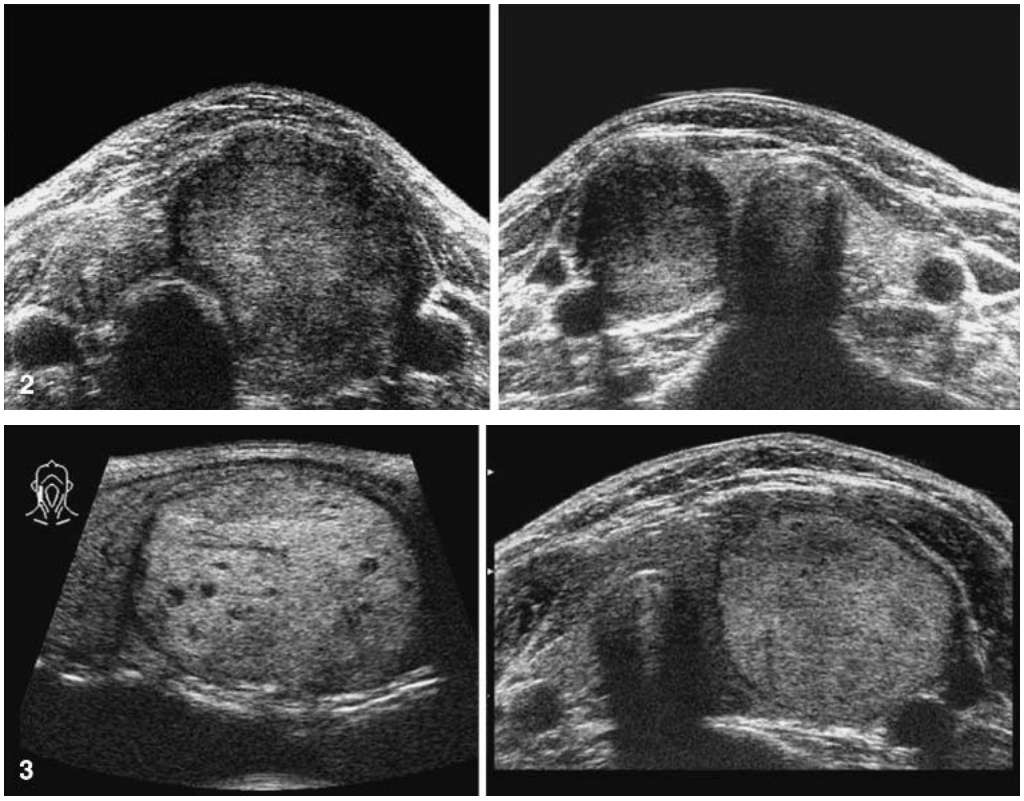


Fig. 2. Ultrasonograms of thyroid follicular carcinoma (detectable cases). **Left.** irregularly shaped solid mass lesion with heterogeneous internal echo in left thyroid lobe. **Right.** round tumor in the right thyroid lobe with low and irregular boundary echogenicity No calcification or cystic degeneration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

Fig. 3. Ultrasonograms of thyroid follicular carcinoma (undetectable cases). **Left.** Oval solid mass with spotty cystic degeneration surrounded by a rim of low echoes (halo sign) in the right lobe of the thyroid. **Right.** Round mass with homogeneous internal echogenicity and regular halo sign in the left lobe of the thyroid. A benign adenomatous nodule was diagnosed by both US and the preoperative clinical examination in these cases.

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

Grade[a]	US B-mode	CD (vascularity)	FFT analysis
1	Benign	None	
2	Benign	Poor (only the peripheral area)	PI < 1.0
3	Follicular neoplastic	Poor to moderate	PI < 1.0
4	Follicular carcinoma	Moderate to rich	PI > 1.0

US: ultrasonography; CD: color Doppler imaging; FFT: fast Fourier transform; PI: pulsatility index.

[a]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).

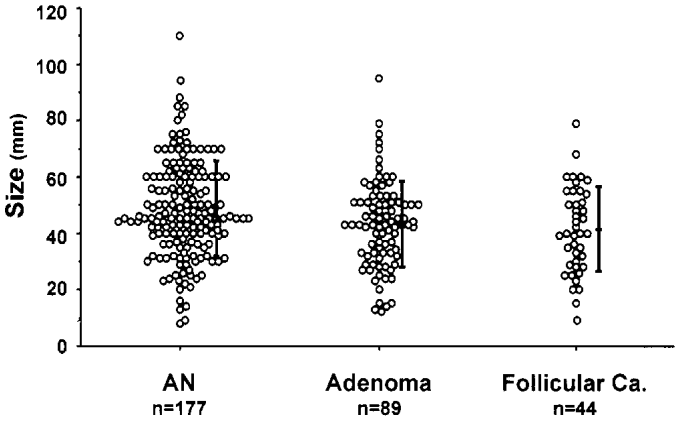


Fig. 4. Differences in maximum tumor diameter according to the histologic classification. No statistically significant differences were found between the cases with an adenomatous nodule (AN), follicular adenoma, or follicular cancer (Ca.) in this series.

Patients and Methods

Color Doppler examination was performed in 310 patients (266 females, 44 males; age range 11–84 years, median 47 years) with a solitary cold nodule in the thyroid gland. All patients underwent surgical resection of the thyroid, and histologic examination was used to confirm the diagnosis. Patients 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). An objective measure of this vascularity is the pulsatility index (PI), which is generated by quantifying blood flow velocity by fast Fourier transformation (FFT) to document the pulsatile nature of the blood flow (PI = Vmax − Vmin/Vmean).

Results

The final histologic diagnosis of the surgical specimens in all 310 cases was an adenomatous nodule in 177 cases, follicular adenoma in 89 cases, and follicular cancer in 44 cases. 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 histologic classifications (Fig. 4). On the basis of the CD exami-

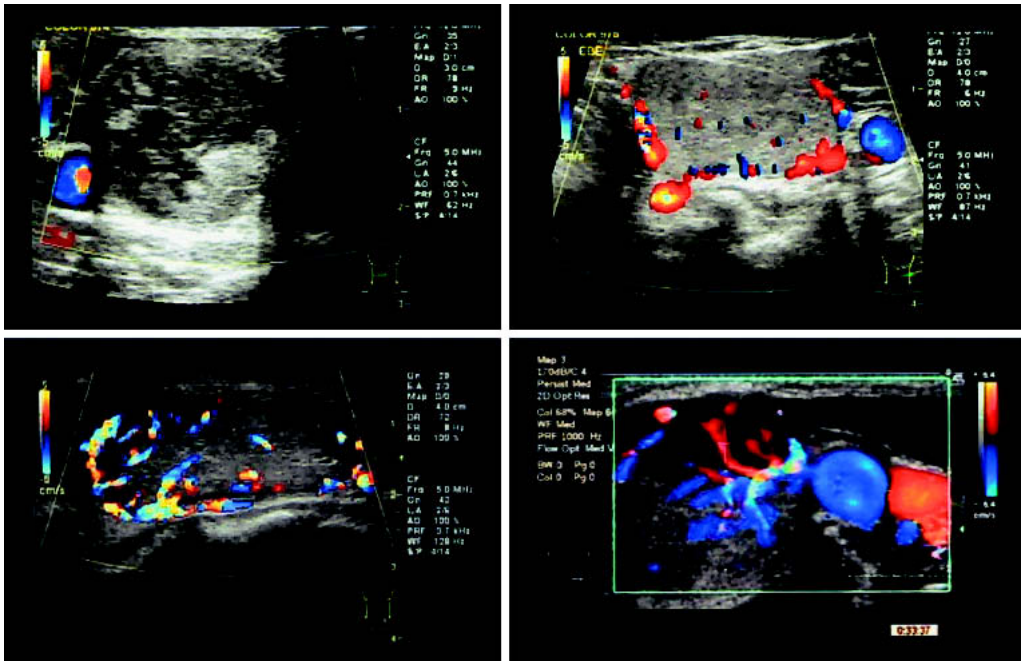


Fig. 5. Characteristic color Doppler (CD) images of lesions with different grading scores (**top left**). Grade 1: There is no color flow mapping (CFM) inside the nodule (**top right**). Grade 2: CFM is seen only in the peripheral area (**bottom left**). Grade 3: blood flow penetrates the tumor, and vascularity was judged to be moderate (**bottom right**). Grade 4: several sources of blood flow penetrate the tumor, and vascularity was judged to be rich. Blood flow analysis revealed high-velocity flow and pulsating feeding vessels with a pulsatility index (PI) of > 1.0.

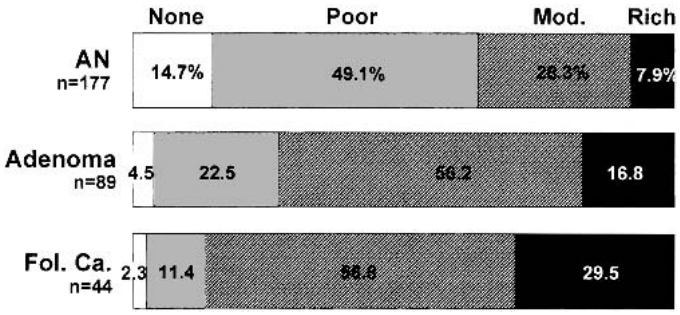


Fig. 6. Tumor vascularity based on the results of the CD examination. Fol. Ca.: follicular cancer; Mod.: moderate.

nation, tumor vascularity was classified as: none, poor, moderate, or rich (Fig. 5). For 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%). Among 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 among 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 statistical differences between adenomatous nodules, follicular adenoma, and follicular cancer ($p < 0.0001$); but analysis of the maximum velocity did not show any statistically differences (Figs. 7, 8).

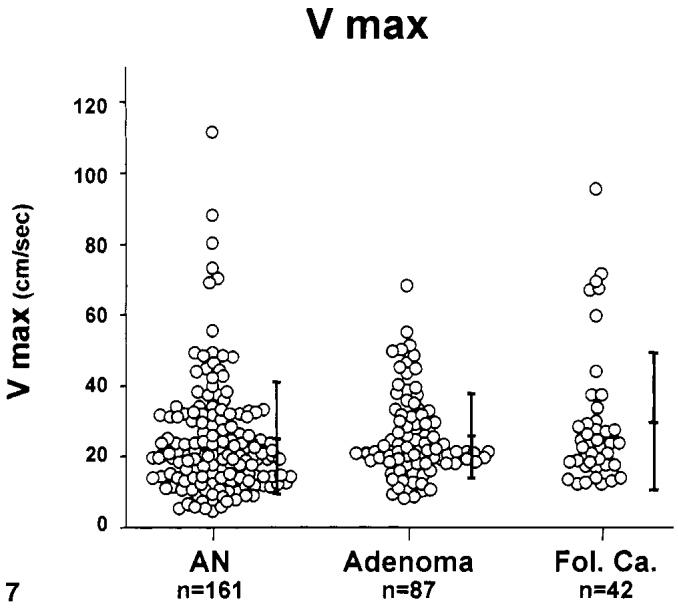
The receiver operating characteristic (ROC) of the PI index of the patients with follicular neoplasms yielded a satisfactory cutoff value of 1.01, specificity of 79.0%, and sensitivity of 69.1% (Fig. 9). The ROC also had an area under curve of 78.0%.

The results of the differential diagnosis by the grading score in this study were as follows: Of the 177 adenomatous nodules, 46.9% were grade 1, 48.0% were grade 2, 5.1% were grade 3, and 0% were grade 4. The corresponding percentages for the 89 follicular adenomas were 16.9%, 49.4%, 30.3%, and 3.4%; and for the 44 follicular cancers they were 0%, 13.6%, 45.5%, and 40.9% (Fig. 10). 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. 11). 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 fine-needle aspiration has yielded satisfactory diagnostic accuracy for thyroid follicular cancer. On the other hand, management for thyroid follicular tumors is now controversial from several viewpoints, including the diagnosis of minimal capsular invasion and the difference between the clinical course, outcome, and histologic diagnosis.

Color Doppler imaging of thyroid tumors is considered useful for observing microvascular structure and vascularity, and it can play an initial and important role in the differential diagnosis, especially for solid tumors without calcification [9, 10]. Some reports claim that CD imaging cannot rule out malignancy or play a role in the differential diagnosis of thyroid cancer [11]. Our series consisted of 310 follicular tumors without papillary carcinoma and yielded results that were different from those in other reports, possibly because we excluded cases with sclerosing or calcified papillary carcinoma from our study. Papillary carcinoma is easily 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 of sclerosing or cal-



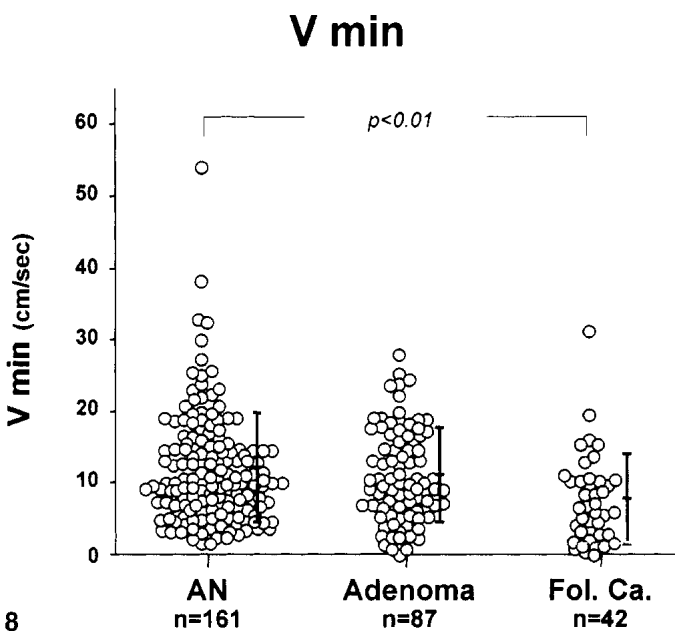


Fig. 7. Blood flow analysis of maximum velocity (Vmax).

Fig. 8. Blood flow analysis of minimum velocity (Vmin).

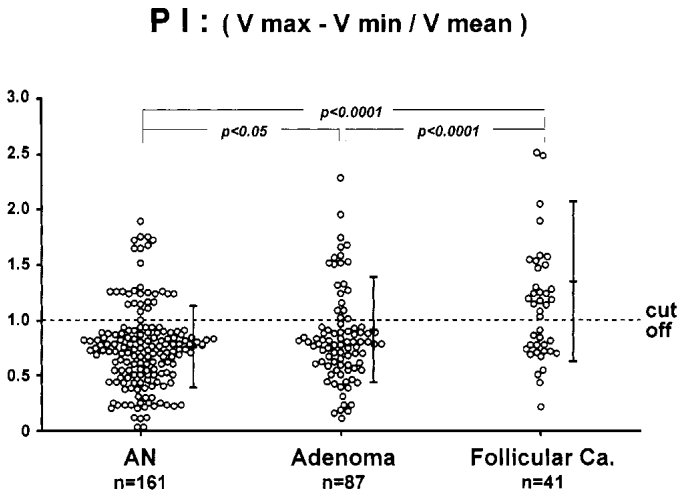
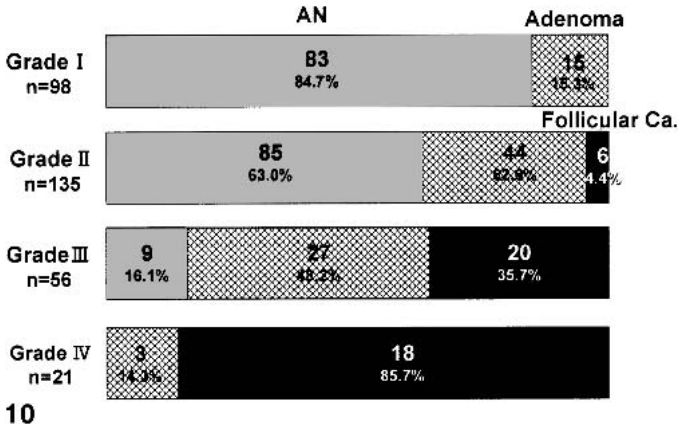


Fig. 9. Differences in the PI index between AN, adenoma, and follicular cancer.



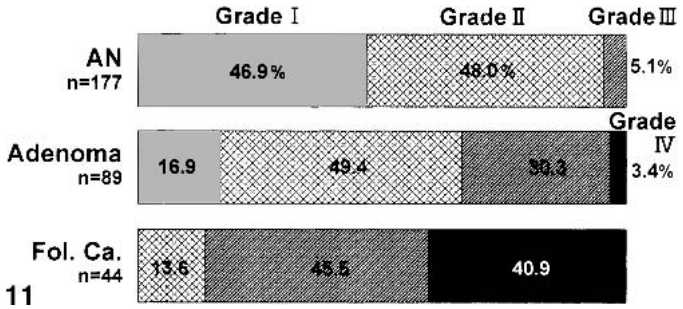


Fig. 10. Results of the differential diagnosis based on the grading score.

Fig. 11. Results of the differential diagnosis based on the histologic type.

cified papillary carcinoma because the Doppler signals are obstructed. CD imaging of thyroid tumors is not useful for diagnosing papillary cancer, but it is clinically useful for diagnosing follicular cancer. Proper indications and use of CD examinations are considered in this article.

The tumor vascularity and the microenvironment of follicular lesions should be evaluated not only by the CD method but also by new histologic approaches. Both US CD, which can visualize hemodynamic features in real time, and confocal laser microscopy, which can reconstruct three-dimensional vascular images, are expected to play an important role in creating a new diagnostic criterion for the diagnosis 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 three-dimensional reconstructions of a variety of biologic specimens. The newly developed microscopic images enable confirmation of the characteristic microvascular structure of thyroid follicular cancer and may lead to a new diagnostic criterion for thyroid follicular cancer.

Conclusions

Color Doppler examination of 310 follicular tumors revealed that high-velocity pulsatile blood flow penetrating the tumor was a char-

acteristic finding of follicular carcinoma. A combination of B-mode US and CD findings, including tumor vascularity and the results of blood flow analysis, have led to the creation of a diagnostic grading system for differentiating 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.

Résumé. L'échographie des glandes thyroïdes a pris une place importante dans le diagnostic des maladies de la thyroïde, et notamment, l'échographie à haute résolution avec la fonction Doppler couleur qui peut mettre en évidence des détails fins de la glande y compris les données hémodynamiques des néoplasies de la thyroïde. La précision de l'échographie peut dépasser les 90% dans le cas de cancer de la thyroïde, surtout pour le cancer papillaire. Cependant, ni l'échographie conventionnelle mode B, ni la cytologie par biopsie à l'aiguille ne fournissent d'aussi bons résultats en ce qui concerne le cancer folliculaire. Le but de cette étude a été d'évaluer l'utilité clinique de l'imagerie Doppler-couleur dans le diagnostic différentiel des lésions folliculaires de la thyroïde. Un examen Doppler couleur a été réalisé chez 310 patients porteurs d'un nodule « froid » solitaire et on a utilisé les donnés d'une échographie mode-B et l'examen Doppler-couleur, y compris la vascularité tumorale et les résultats de l'analyse FFT pour catégoriser les lésions comme suit: Grade 1, lésion folliculaire bénigne [aucun débit couleur à l'intérieur du nodule (CFM)]; Grade 2, type périphérique bénin (CFM seulement en périphérie, PI < 1.0); Grade 3, suspicion de cancer folliculaire (CFM pénétrante, vascularité modérée); Grade 4, cancer folliculaire (CFM à haute vélocité pénétrante, PI 1.0). Tous les patients ont eu une résection chirurgicale et le diagnostic a été confirmé par l'examen anatomopathologique. Pour les 177 nodules adénomateux, les gradations ont été: Grade 1, 46.9%; Grade 2, 48.0%; Grade 3, 5.1%; et Grade 4, 0%. Les pourcentages correspondants pour les 89 adénomes folliculaires ont été, respectivement, de 16.9%, 49.4%, 30.3% et 3.4%; et ceux pour les 44 cancers folliculaires ont été de 0%, 13.6%, 45.5% et 40.9%. En assumant que les lésions Grades 1 et 2 sont bénignes et que les lésions Grades 3 et 4 sont malignes, 38 des 44 cancers folliculaires et 227 des 266 tumeurs bénignes ont été diagnostiqués correctement, ce système de gradation a eu une sensibilité de 88.9%, une spécificité de 74.2% et une précision de 81.0%. L'examen par Doppler-couleur des 310 tumeurs folliculaires a montré que le débit pulsatile à haute vélocité pénétrant la tumeur est une caractéristique du cancer folliculaire et que cet examen peut fournir des critères diagnostiques intéressants. Le système de gradation diagnostique différentiel pour cet examen et les résultats de l'analyse FFT peuvent avoir un intérêt dans le diagnostic. L'échographie avec la fonction Doppler-couleur peut avoir un rôle important dans le diagnostic différentiel des tumeurs de la thyroïde.

Resumen. La ultrasonografía de la glándula tiroides ha demostrado ser un método de diagnóstico clínico útil, y el recientemente desarrollado mapeo funcional de flujo con ultrasonografía con Doppler a color de alta resolución puede revelar detalles finos de la glándula tiroides y diferenciar las características hemodinámicas de los neoplasmas tiroideos. La ultrasonografía puede alcanzar una certeza diagnóstica de 90% en el carcinoma tiroideo, especialmente en el carcinoma papilar. Sin embargo, ni la ultrasonografía de modo B convencional ni la citología por aspiración con aguja fina han dado resultados satisfactorios en el carcinoma folicular. El propósito del presente estudio fue evaluar la utilidad clínica de la imaginología por Doppler a color en el diagnóstico diferencial de lesiones foliculares. Se practicó Doppler a color en 310 pacientes con nódulo solitario, utilizando una combinación de los resultados del US modo B y del Doppler a color, incluyendo la vascularidad tumoral y los resultados de la aspiración con aguja fina para crear el siguiente sistema de gradación para el diagnóstico diferencial de las lesiones foliculares: Grado 1, lesión folicular benigna (no hay mapeo de flujo a color [MFC] en el interior del nódulo); Grado 2, benigno de tipo periférico (MFC sólo en el área periférica, PI < 1.0); Grado 3, sospecha de carcinoma folicular (MFC penetrante, vascularidad moderada); Grado 4, carcinoma folicular (MFC penetrante de alta velocidad, PI > 1.0). Todos los pacientes fueron sometidos a resección quirúrgica, y el examen histológico fue utilizado para confirmar el diagnóstico. La gradación de los 177 nódulos adenomatosos fue: Grado 1, 46.9%; Grado 2, 48%; Grado 3, 5.1%; y Grado 4, 0%. Los correspondientes porcentajes para los 89 adenomas foliculares fueron 0%, 13.6%, 45.5% y 40.9%. Bajo la asunción de que las lesiones Grados 1 y 2 son benignas y que las Grados 3 y 4 son malignas, 38 de 44 carcinomas foliculares y 227 de 266 tumores benignos fueron diagnosticados correctamente, lo cual significa una sensibilidad de 88.9%, una especificidad de 74.2% y una certeza de 81% para el sistema de gradación. El examen por imaginología con Doppler a color de 310 tumores foliculares reveló que un flujo sanguíneo pulsátil de alta velocidad que penetra el tumor es un hallazgo característico del carcinoma folicular y que el método representa un nuevo criterio diagnóstico en la imaginología por Doppler a color. La gradación diferencial diagnóstica de los exámenes con Doppler a color y los resultados de la aspiración con aguja fina puede demostrar utilidad diagnóstica. El ultrasonido con la función de Doppler a color puede jugar un papel importante en el diagnóstico diferencial de los tumores tiroideos.

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