Int J Clin Exp Med 2018;11(3):2331-2336
www.ijcem.com /ISSN:1940-5901/IJCEM0072647

Original Article

An analysis of the clinical value of high-frequency color Doppler ultrasound in the differential diagnosis of benign and malignant thyroid nodules

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Received January 12, 2018; Accepted February 23, 2018; Epub March 15, 2018; Published March 30, 2018

Abstract: Objective: To investigate the clinical value of high-frequency color Doppler ultrasound (HFCDU) in the differential diagnosis of benign thyroid nodules and thyroid carcinoma. Methods: A total of 92 patients treated in Pudong New Area People's Hospital for thyroid nodules from June 2015 to July 2016 were recruited as subjects. All of them underwent HFCDU tests before surgery and received the postoperative pathological diagnosis which was used as the gold standard. The results obtained from HFCDU and pathological examination for the differential diagnosis of benign and malignant thyroid nodules were compared and analyzed. Meanwhile, the size, shape, boundary, internal echo, internal and surrounding blood flow signal of these two types of nodules were examined for comparison. Results: There were 107 nodules in 92 patients. The sensitivity, specificity, and accuracy of HFCDU were 93.55%, 86.67% and 90.65% respectively. The value of the areas under the curve (AUC) calculated from the receiver operating characteristic (ROC) curve was 0.923, and the 95% confidence interval (CI) was 0.886-0.967. The differences in boundary, shape, aspect ratio, internal echo, posterior echo, calcification and other indices between benign and malignant thyroid nodules were significant (P<0.05). The result from the multi-variant logistic regression analysis showed that factors such as unclear boundary, irregular shape, aspect ratio > 1, blood flow > grade 2, and uneven internal echo were all correlated with thyroid nodule malignancy. Conclusion: HFCDU can be applied clinically for the differential diagnosis of benign and malignant thyroid nodules as it has high sensitivity, specificity and can present clear imaging features.

Keywords: High-frequency color Doppler ultrasound, thyroid, benign nodule, thyroid carcinoma

Introduction

Thyroid carcinoma is one of the most common malignant tumors clinically, and its incidence and mortality rates have been increasing each year [1]. Since its clinical symptoms during early stage are quite unnoticeable, most cases of this disease are often discovered at middle or late stage, which makes the patients miss the best time for surgical cure, and severely threatens their health and life [2]. Hence, it is of great importance to find an effective diagnostic method for the early detection of thyroid carcinoma, so that patients' survival rate can be improved [3]. In the past, the conventional ultrasound was adopted as a main diagnostic tool for diagnosing benign and malignant thyroid nodules in clinic, but its accuracy was not good enough, as the results were often affected by various factors, such as examiner's skill level. However, due to the continuous development of medical technology and sonography, people have begun to apply color Doppler ultrasound in the clinical diagnosis of benign and malignant lesions, and have achieved quite good outcomes [4, 5]. This study aimed to investigate the diagnostic value of high frequency color Doppler ultrasound (HFCDU) in the differential diagnosis of benign thyroid nodules and thyroid carcinoma, and to provide some useful information for supporting its extensive clinical application.

Materials and methods

Case selection

The study retrospectively analyzed a total of 92 patients who were treated in Pudong New Area People's Hospital for thyroid diseases and received both HFCDU and pathological diagnosis from June 2015 to July 2016. All patients signed informed consents and the study was approved by the Ethic Committee of Pudong New Area People's Hospital.

Inclusion criteria: 1) Patients with thyroid diseases underwent both HFCDU and pathological diagnosis; 2) Patients were willing to cooperate with the treatment; 3) Patients' medical records were complete.

Exclusion criteria: 1) Patients had other severe thyroid diseases in addition to thyroid nodules, or the acoustic halo couldn't be detected in thyroid nodules; 2) Patients experienced recurrence of malignant thyroid nodules after surgery, or had hyperplasia of one thyroid lobe caused by the hypoplasia of thyroid and parathyroid in the opposite lobe; 3) Patients had benign thyroid nodules generated by the scar and proliferation of the residual thyroid tissue or other factors after treatment.

Examination methods

The high-frequency ultrasound diagnosis was performed by SIMENS Acuson Antares and Mindray DC-Expert II, and the standard diagnostic procedure was implemented. Patients were lying in supine position on the examination bed, with shoulders elevated by pillow and head tilted backwards to expose the front neck area. The frequency of the ultrasound probe was 3.5 MHz. Two physicians who were experienced in thyroid inspection by high-frequency ultrasound worked together to measure and describe patients' imaging features presented by color Doppler ultrasound. Meanwhile, the blood flow in patients' thyroid, nodules and their surrounding area were examined by color Doppler flow imaging (CDFI). All patients received surgical treatments correspondingly after the diagnosis, and the surgical pathological examination was set as the gold standard.

Patients' characteristics

Patients' age, gender, course of thyroid disease, treatment history, results of color ultrasound and pathological diagnosis, and values of various indices, such as thickness, integrity and blood flow of the acoustic halo, were obtained for the study.

The nodular goiters usually contain more than two nodules with the following features: irregular shape, no presence of capsule or calcification, low or mixed internal echo, no change in posterior echo, no enlarged peripheral lymph node, blood flow signal at grade 0-1, maximum velocity of blood flow at 26.84±11.07 cm/s and resistance index at 0.51±0.11.

The thyrophyma usually contains single nodule, with features as follows: regular shape, presence of capsule, low internal echo, no calcification, enhanced posterior echo, no enlarged peripheral lymph node, blood flow signal at grade 0-1, maximum velocity of blood flow at 29.09±10.23 cm/s and resistance index at 0.54±0.05.

The thyroid cyst normally contains single nodule, with regular shape, presence of capsule, no internal echo, no calcification, enhanced posterior echo, no enlarged peripheral lymph node and blood flow signal at grade 0.

The thyroid carcinoma usually contains single nodule, with irregular shape, no capsule, low or mixed internal echo, with or without calcification or peripheral lymph node swelling, no change or attenuation in posterior echo, blood flow signal at 1-3 grade, maximum velocity of blood flow at 40.02±21.03 cm/s and resistance index at 0.71±0.03.

Outcome measures

The shape, boundary, aspect ratio, internal echo, posterior echo, calcification and blood flow of thyroid were checked and the results were recorded. The blood flow signal of nodules was rated according to Adler semi quantitative classification [6]. Grade 0, no visible blood flow signal; grade 1, no more than 2 visible punctate blood flow signals; grade 2, one visible blood vessel or 3-4 punctate blood flow signals; grade 3, more than 1 visible blood vessel or more than 4 punctate blood flow signals. Criteria for defining benign and malignant nodules by HFCDU were based on the malignancy risk-stratification in the guidelines for thyroid carcinoma by American Thyroid Association in 2015 [7]. According to nodules' suspicious features shown in image, the risk of malignancy can be classified into five levels: high suspicion of malignancy, intermediate suspicion of malignancy, low-suspicion of malignancy, very low suspicion of malignancy and benign. The pathological diagnosis was set as the gold standard. The accuracy, sensitivity and specificity of HFCDU in the differential diagnosis were observed for analysis.

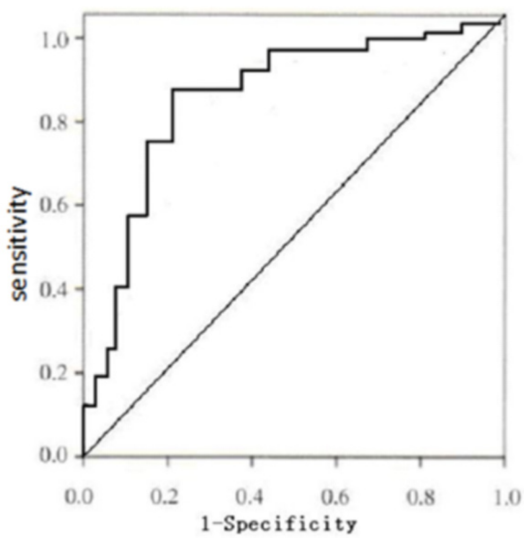

Figure 1. The ROC curve for HFCDU in diagnosing benign and malignant thyroid nodules. HFCDU, high-frequency color Doppler ultrasound.

Table 1. Comparison of results of HFCDU and pathological examination

HFCDU	Pathological examination		Total amount
	Benign	Malignant	
Benign	58	6	64
Malignant	4	39	43
Total	62	45	107

Note: HFCDU, high-frequency color Doppler ultrasound.

Statistical analysis

Statistical software SPSS 26.0 was applied for the data analysis. The count data were expressed by constituent ratio (%), and the comparison between groups was performed by X^2 test; the quantitative data were presented by mean ± standard deviation, and the comparison between groups was performed by t test. In order to evaluate the diagnostic value of the HFCDU, the values of the areas under the curve (AUC) were calculated from the receiver operating characteristic (ROC) curve. A value of $P<0.05$ was considered as statistically significant.

Results

Patients' characteristics

Among the 92 patients, there were 33 males and 59 females, who were aged 40-78 (62.5±5.0 years). Patients' course of disease lasted for 1-8 years (5.5±2.0 years). The total number of thyroid nodules was 107, of which there were 84 solitary nodules and 23 multiple nodules. There were 43 cases where nodules were at the left lobe and 64 cases at the right lobe. The biggest lesion was 42 mm × 37 mm × 25 mm in size, while the smallest one was 12 mm × 7 mm × 5 mm. Pathological results: There were 62 benign cases (adenoma 7, adenomatous goiter 8, nodular goiter 47) and 45 malignant cases (papillary carcinoma 37, medullary carcinoma 2, follicular carcinoma 2, undifferentiated carcinoma 3, lymphoma 1).

The ROC curve of the HFCDU examination

The ROC curve was plotted using sensitivity as ordinate and 1-Specificity as abscissa, and values of AUC were calculated accordingly. The AUC for HFCDU in diagnosing the nature of thyroid nodules was 0.923, and the 95% confidence interval (CI) was 0.886-0.967 (**Figure 1**).

Comparison of the results by HFCDU and pathological examination

It can be seen from the results that the sensitivity, specificity, and accuracy of HFCDU were 93.55% (58/62), 86.67% (39/45) and 90.65% (97/107) respectively (**Table 1**).

Correlation between HFCDU indices and pathological examination in the differential diagnosis of benign and malignant thyroid nodules

The results of HFCDU showed that there were statistically significant differences in the boundary, size, aspect ratio, internal echo, posterior echo, calcification and other indices between benign and malignant thyroid nodules (all $P<0.05$). See **Table 2**, **Figures 2** and **3**.

Indices that are correlated with malignant thyroid nodules

The multi-variant logistic regression analysis was conducted for indices including boundary, shape, aspect ratio, internal echo, posterior echo, blood flow and presence of calcification. The result showed that unclear boundary, irregular shape, aspect ratio > 1, blood flow > grade 2, and uneven internal echo were correlated with the thyroid nodule malignancy (**Table 3**).

Table 2. Comparison of ultrasound indices in benign and malignant nodules (n, %)

Sonographic features		Malignant (n=45)	Benign (n=62)	X^2 value	*P* value
Boundary	Clear	6 (13.33)	46 (74.19)	23.182	0.000
	Unclear	39 (86.67)	16 (25.81)		
Shape	Irregular	38 (84.44)	29 (46.77)	8.134	0.004
	Regular	7 (15.56)	33 (53.23)		
Aspect ratio	≤ 1	15 (33.33)	49 (79.03)	23.578	0.000
	> 1	30 (66.67)	13 (20.97)		
Internal echo	Even	5 (11.11)	35 (56.45)	20.075	0.000
	Uneven	40 (88.89)	27 (43.55)		
Posterior echo	No attenuation	26 (57.78)	49 (79.03)	8.428	0.004
	Attenuation	19 (42.22)	13 (20.97)		
Calcification	Yes	22 (48.89)	11 (17.74)	13.022	0.000
	No	23 (51.11)	51 (82.26)		
Blood flow	Grade 0	3 (6.67)	25 (40.32)	9.254	0.007
	Grade 1	8 (17.78)	19 (30.65)		
	Grade 2	15 (33.33)	10 (16.13)		
	Grade 3	19 (42.22)	8 (12.90)		

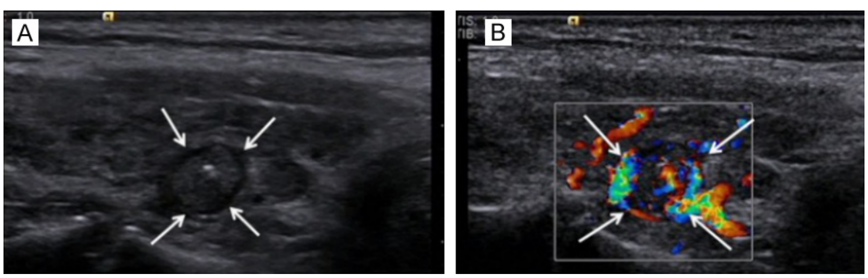

Figure 2. Sonographic features of nodular goiter. A. Regular boundary of the nodule and low echo found by two-dimensional ultrasound; B. Blood flow signal in nodule observed by color Doppler ultrasound.

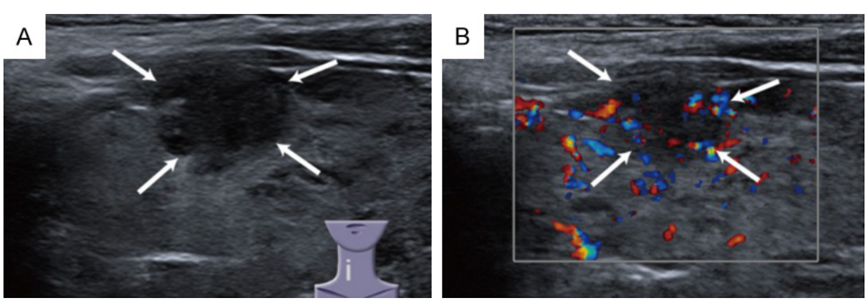

Figure 3. Sonographic features of thyroid papillary carcinoma. A. Irregular boundary of the nodule and low echo found by two-dimensional ultrasound; B. High blood flow signal around nodule caught by color Doppler ultrasound.

Discussion

The incidence and mortality rates of thyroid carcinoma are quite high. Most of the patients don't have any noticeable symptoms during the early stage, and the disease is often discovered when it already reaches middle or late stage, which makes the patients miss the best time for the surgical cure [8, 9]. Therefore, for patients with thyroid carcinoma, an effective early diagnosis and a timely treatment can be important means to improve the prognosis. At present, ultrasound is commonly used as an imaging method for differentiating benign and malignant thyroid nodules in clinic, but the conventional two-dimensional ultrasound technique still has some limitations [10]. With the rapid development of sonography, HFCDU has been gaining increasing po-pulation in the clinical practice.

In this study, there were 107 nodules in 92 patients. The pathological examination was set as the gold standard, and the sensitivity, specificity and accuracy of HFCDU in the differential diagnosis of benign and malignant nodules were 93.55%, 86.67% and 90.65% respectively, indicating that HFCDU combined with two-dimensional ultrasound can deliver a quite satisfactory result in terms of sensitivity and specificity, which aligned with other people's findings

Table 3. Indices that are correlated with thyroid nodule malignancy

Variant	*P* value	OR value	95% CI
Unclear boundary	0.081	1.043	0.619-2.906
Irregular shape	0.088	0.991	0.147-0.942
Aspect ratio > 1	0.004	2.816	2.736-6.002
Posterior echo	0.437	1.385	0.813-1.253
Presence of calcification	0.257	0.996	0.803-1.104
Blood flow > grade 2	0.003	2.204	1.724-6.335
Uneven internal echo	0.002	2.306	2.431-5.997

Note: CI, confidence interval.

[11-15]. Meanwhile, the shape and boundary of benign nodules were quite different from malignant ones, and there was no apparent acoustic halo, presence of calcification or rich blood flow in benign nodules as opposed to malignant thyroid nodule, indicating that the high-frequency sonographic features of these two types of thyroid nodules are quite clear and different. This might be due to the fact in thyroid carcinoma, the infiltrative growth in malignant tumor can make the boundary looked unclear and fuzzy (angular and microlobulated). However, since the sample size in the present study was relatively small, research with a larger sample size would be necessary in the future for further verification. In healthy thyroid tissue, there is usually homogeneous low to intermediate level of echo, while in thyroid nodules, there can be abnormalities in acoustic halo, echo, calcification and blood flow. In addition, the benign nodule usually has a comparatively regular shape, clear boundary and little internal blood flow distribution, while the blood flow in the malignant one is quite high [16-18]. In recent years, there have been many clinical studies demonstrating that the imaging features of the thyroid nodules, such as irregular shape, fuzzy boundary, low internal echo, micro-calcification, rich blood flow, are closely related to the level of malignancy, which can be regarded as high-risk factors of malignant thyroid lesions [19-24]. Therefore, it can be suggested that the high-frequency ultrasound can provide more reliable basis for the clinical diagnosis of benign and malignant thyroid nodules.

As an investigative study, there were still some shortcomings. First of all, the standard need to be further improved and refined, in order to avoid the overlapping of total scores of benign and malignant lesions and enhance the specificity and accuracy of the diagnosis; secondly, a prospective study with a larger sample size would be necessary for further verification; lastly, this study only investigated the performance of HFCDU in the diagnosis of thyroid nodules, while other methods were not involved for comparison and analysis, this might become a research topic for us to pursue in the future.

In conclusion, HFCDU can serve as a major method for diagnosing thyroid nodules, and has high value when being applied for the differential diagnosis prior to the operation. Clinically, the diagnostic accuracy can be improved by including indices such as shape, internal echo, calcification, posterior echo, blood flow signal of the nodule.

Acknowledgements

This work was supported by Academic Leaders Project of Shanghai Pudong New Area Health System (PWRd2017-06); Funding for Major Weak Disciplines of Shanghai Pudong New Area Health System (PWZbr2017-10).

Disclosure of conflict of interest

None.

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