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The Value of Contrast-Enhanced Ultrasound and Acoustic Pulse Radiation Force Imaging in the Differentiation of Benign and Malignant Thyroid Nodules

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Abstract: Objective: To explore The Value of Contrast-enhanced Ultrasound and Acoustic Radiation Force Pulse Imaging for The Differentiation of Benign and Malignant Thyroid Nodules, and to seek the best imaging method for the early differential diagnosis of thyroid nodules. Methods: The imaging information of 107 benign and malignant thyroid nodules in 78 patients were retrospectively analyzed and compared, all cases simultaneously conducted ARFI (acoustic radiation force impulse imaging technology) and CEUS examinations before operation. Taking pathological results as gold standard, the accuracy rate of ultrasound contrast, elastography and combined application of contrast-enhanced ultrasound and acoustic pulse radiation force imaging in the diagnosis of benign and malignant thyroid nodules was evaluated, and the sensitivity, specificity and accuracy of the two examinations were compared. Results: The sensitivity, specificity and accuracy of conventional ultrasound in diagnosing thyroid nodules were 45.16%, 46.05% and 66.36%, respectively. The sensitivity, specificity and accuracy of elastography in diagnosing thyroid nodules were 51.61%, 53.95% and 78.50%, respectively. The combined application of contrast-enhanced ultrasound and acoustic pulse radiation force elastography has a sensitivity of 87.71%, specificity of 94.74% and accuracy of 98.13%. Among 107 thyroid nodules, 58 were benign, most of which had an elastography score of 3 or less, and most of which showed yellowish green. The benign nodules were mainly homogeneous enhancement or high enhancement, later than the normal thyroid tissue. Conclusion: ARFI and CEUS have high value in differential diagnosis of benign and malignant thyroid nodules ,the combined application of two methods can be helpful to improve the diagnostic accuracy, which provides the basis for subsequent treatment programs and is worthy of clinical application.

1. Introduction

Thyroid nodule and thyroid cancer are two common diseases in oncology department. Among them, thyroid nodule refers to a mass existing in thyroid gland, which can be single or multiple. The incidence of multiple nodules is high, while the canceration rate of single nodule is high[1]. The incidence of thyroid cancer in the world is increasing year by year, with an annual increase of about 4%. In the past 30 years, the incidence of thyroid cancer in the world is increasing year by year, and the incidence of thyroid cancer in China is also on the rise [2]. In 2015, the number of new cases and deaths in China accounted for 15.6% and 13.8% of the world's total. The deaths occurred mainly in Asia. The mortality rate of thyroid cancer is 0.34/100,000, male 0.23/100,000, female 0.46/100,000 [3]. It has long been one of the tumors that have attracted much attention. Although ultrasonic examination has become the primary examination method for thyroid nodules, the contents of ultrasonic research are still mainly focused on the two-dimensional morphology of thyroid masses, color Doppler blood flow signals, flow velocity and resistance index, etc[4]. The above indexes can be complex and diverse, and benign and malignant lesions have certain overlapping on the ultrasonic images, which increases the difficulty of differential diagnosis of benign and malignant thyroid nodules [5]. Supersonic examination has become an important

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method for thyroid diseases due to its advantages of simplicity, economy, sensitivity and non-radioactivity. Therefore, this study combines contrast-enhanced ultrasound with Acoustic pulse radiation force elastography to explore its value in differential diagnosis of benign and malignant thyroid nodules.

2. Materials and Methods

2.1 Research Object

78 patients with 107 nodules were selected from December 2017 to December 2019, who came to our hospital for Contrast-enhanced ultrasound and acoustic pulse radiation force elastography and were hospitalized for surgery. Among them, there were 43 males, aged 24-64 years, with an average age of (47.5.±12.9) years. 35 women, aged 22-71 years old, average (47.5±13.1) years old. According to the TI-RAD 5 classification standard proposed in 2011, patients with thyroid nodules were classified.

Selection criteria: (1) solid nodule (nodule cystic fraction < 30%); (2) Conventional ultrasound diagnosis of hypoechoic nodules; (3) 20mm ⩾ Nodules ⩾ 5 mm; (4) Confirmed by histopathological examination.

Exclusion criteria: (1) Patients with thyroid dysfunction, such as Hashimoto's thyroiditis, hyperthyroidism/hypothyroidism, etc., as a result of laboratory examination or pathology; (2) Thyroid nodules located at isthmus, close to the carotid pulse or protruding to capsule obviously.

2.2 Instruments and Reagents

Germany Siemens Acuson S3000 ultrasound diagnostic instrument Equipped with ARFI imaging technology and CEUS software, using linear array probe 9L4, probe frequency is 4-9 MHz, equipped with VTQ, VTIQ and real-time contrast matching imaging technology, imaging mechanical index (MI) is 0.1, The probe resolution is 0.1 mm. Choose Bracc as a contrast agent, dilute SonoVue produced by the company with 5 ml of saline, and shake it well to prepare a microbubble suspension for later use.

2.3 Inspection Method

VTQ (Virtual touch tissue quantification) check: Apply sufficient amount of disaster mixture on the probe, scan longitudinally to obtain the maximum section of nodule, use slight pressure to make the probe perpendicular to the surface of lesion, require the patient to hold his breath, do not swallow, and perform VTQ examination. The sampling frame is placed in the region of interest (ROI) of the nodule. The left side of the screen is a two-dimensional ultrasound image, and the right side is VTQ to measure the shear wave velocity of the nodule. Each nodule is measured 7 times, the maximum and minimum values are removed, and the average and median values of the five measurements are taken. During measurement, great vessels of the neck should be avoided as much as possible to avoid interference of carotid pulsation, and calcification, liquefaction and necrosis areas should be avoided as much as possible to avoid large deviation of measured values and affect diagnostic accuracy. When the SWV value displayed by the instrument is X. XXm/s, it is called “no value”. After excluding the influence of physiological activities such as respiration and swallowing, if there is still no measured value, there are two possibilities. One is that the lesion is cystic and VTI can be used for auxiliary diagnosis. If it is white, the texture is softer and it is presumed to be cystic. It can be treated as Om/s here. Secondly, the lesion tissue is too hard, such as calcification, which exceeds the measurement range of the instrument. -9m/s, mark SWV here as 9m/s for processing.

VTIQ (Virtual touch tissue imaging and quantification) inspection: Then perform VTIQ inspection, and still select the largest section of the lesion. When the lesion is most clearly displayed, instruct the patient to hold his breath and enter the VTIQ mode, focusing on analyzing the VTIQ quality and speed mode diagram. In the quality chart, green indicates high quality chart, yellow and red indicate medium and low quality respectively. When the quality map is the highest, that is, when the image is all green, adjust to the velocity map mode, place the sampling frame in different areas inside the lesion, with the ROI minimum of lmmX1 mm, obtain multiple groups of SWV in the effective measurement area of the lesion, remove one of the highest and lowest values, and take the average and median values for the rest, with the unit of m/s.

CEUS (contrast-enhanced ultrasound) examination: contrast agent SonoVue lyophilized powder produced by Bracco, Italy, usage: add 25mg SonoVue into 5ml normal saline, shake continuously for 30s to form microbubble suspension. Two dimensional ultrasound was used to select the best display section of the focus. Normal thyroid gland tissue was required around the focus. The probe was fixed perpendicular to the surface of the focus, and the patient was instructed not to swallow the contrast pulse sequence (CPS) mode of contrast-enhanced ultrasound imaging was initiated. The contrast agent was injected by 20g trocar through the anterior elbow vein of the upper extremity. Each injection was 2.4ml, followed by the rapid push of 5ml saline into the tube. At the same time, press the timer and the dynamic storage key, use the two image mode to dynamically observe the perfusion of the focus and the echo intensity change compared with the surrounding normal glands in real time, record the time of entering, reaching the peak, peak intensity and fading time of the contrast, and store the dynamic image in the ultrasonic hard disk. Before the injection of contrast agent, the patient should be asked if he has a history of allergy and signed the informed consent of the patient, and the corresponding emergency measures should be prepared. After the contrast-enhanced ultrasound examination, the patient was asked to stay for 30 minutes.

2.4 Statistical Method

SPSS 23.0 and MEDCALC software were used for statistical analysis. SWV measured by VTIQ technology is the measurement data, expressed by ($\bar{x} \pm s$); T test was used to compare the difference of SWV values between benign nodules and malignant nodules. Drawing receiver operating characteristic curve to Determine the Best Diagnostic Boundaries of VTI Hardness Grading Method, VTI Area Ratio Method and VTIQ SWV for Differentiating Benign and Malignant Thyroid Nodules.

3. Result

3.1 Pathological Results

Of 107 thyroid nodules confirmed by surgery or biopsy, 58 are benign (44 nodular goiter and 14 thyroid adenoma); 49 malignant nodules (46 papillary carcinomas and 3 medullary thyroid carcinomas).

3.2 Vti Technical Diagnosis Results

VTI elastic images of thyroid nodules are classified as follows: Class I: nodule area is completely white or a little dotted black with white area > 95%; Class II: The nodule area is mostly white, a small part is black, and the white area is between 50% and 95%. Class III: Nodular area has the same proportion of black and white, with white area accounting for 50%; Grade IV: Nodular area is mostly black, a small part is white, and the black area is between 50% and 95%; Grade V: Nodular area is almost completely black with a small amount of punctate white, with black area > 95%; Grade VI: Nodular area is all black with black area > 99%. VTI hardness classification (Table 1). The cutoff value of VTI grading method for distinguishing benign and malignant thyroid nodules is grade 3, and the area under the curve is 0.82. The cutoff value of VTI area ratio method for differentiating benign and malignant thyroid nodules is 1.00, and the area under the curve is 0.80 (Table 2).

Table 1 Vti Hardness Grading of Thyroid Nodules

VTI rating	I	II	III	Ⅳ	V	Ⅵ	Total	
Benign	2	20	14	9	4	0	49	
Malignant	0	1	8	27	18	4	58	
Total	2	21	22	36	22	4	107	

Table 2 the Diagnostic Value of Vti and Vtiq in Differentiating Benign and Malignant Thyroid Nodules (%)

Inspection method	AUC	95%CI	Truncated value	Sensitivity	Specificity	PPV	Accuracy rate
VTI hardness grading	0.803	0. 771 -0.812	2	80.01	76.05	8S 48	79.36
VTI area ratio	0.815	0.734-0.861	1.33	92.34	66.80	8L 02	84.05
VTIQ SWV average	0.711	0.681-0.749	2.86	72.37	68.937	74.78	69.33
VTIQ SWV maximum	0.587	0.607-0.762	3.01	60.13	69.17	72 45	61.52

Note: SWV is shear wave velocity; VTIQ is a tissue quantification technique for palpation. VTI is a tissue imaging technique for palpation. AUC is the area under the curve; 95%CI is 95% confidence interval; PPV is positive predictive rate; NPV is negative predictive rate.

3.3 Vtiq Technical Diagnosis Results

The average VTIQ SWV of benign nodules was 2.65±0.57, and the average VTIQ SWV of malignant nodules was 3.28±0.94. The maximum VTIQ SWV of benign nodules is 3.05±0.70, and the maximum VTIQ SWV of malignant nodules is 3.87±1.38. The SWV values of malignant nodules were greater than benign nodules, and the differences were statistically significant ($P<0.05$).

3.4 Ceus Diagnostic Results

There are different modes of contrast-enhanced ultrasonography in root thyroid nodule. Ring enhancement and high enhancement are usually used as the diagnostic criteria for benign nodule, while uneven and low enhancement are used as the diagnostic criteria for malignant nodule. The sensitivity, specificity, accuracy, positive predictive value and negative predictive value of CEUS in diagnosing benign and malignant thyroid nodules are 68.1%, 76.86%, 70.7%, 66.1% and 75.33% respectively.

3.5 Results of Combined Examination of Contrast-Enhanced Ultrasound and Ultrasound Elastography

Of 107 nodules, 76 were benign and 31 were malignant. The sensitivity of ultrasonic elastography alone is higher than that of high-frequency color Doppler ultrasound alone, and the difference is statistically significant ($p < 0.05$). There was no significant difference in sensitivity, specificity and accuracy between high-frequency color Doppler ultrasound and ultrasonic elastography alone ($p > 0.05$). The combined detection sensitivity, accuracy and precision of Contrast-enhanced Ultrasound and acoustic radiation force pulse imaging are higher than those of conventional ultrasound and ultrasound elastography, and Contrast-enhanced Ultrasound, the difference is statistically significant ($p<0.05$). See Table 3.

Table 3 Comparison of Diagnostic Value of Contrast-Enhanced Ultrasound, Ultrasound Elastography and Their Combined Detection for Thyroid Nodules (%)

Inspection method	Sensitivity	Specificity	Accuracy
Contrast-enhanced ultrasound examination	45.16(14/31)#	46.05(35/76)	66.36(71/107)
Elastic imaging technology	51.61(16/31)*	53.95(41/76)	78.50(84/107)
Combined detection of the two	87.71(27/31)*#	94.74(72/76)*#	98.13(105/107)*#

Note: * compared with high frequency color Doppler ultrasound, $p < 0.05$; # compared with ultrasonic elastography, $p < 0.05$

4. Discussion

Ultrasonography is the preferred method for clinical diagnosis of thyroid nodules [6]. In recent years, ultrasound has developed rapidly in the diagnosis of benign and malignant thyroid nodules, especially in the extensive application of contrast-enhanced ultrasound and acoustic pulse radiation force Imaging. A total of 107 patients with 78 benign and malignant thyroid nodules were examined by ultrasound in this study. Ultrasound manifestations of thyroid malignant nodules are: irregular nodule shape, no capsule, unclear boundary, uneven internal echo and punctate or gravel calcification. Palpation showed that the incidence rate of nodular thyroid nodules was 4%~8%, and the incidence rate of thyroid nodules examined by high-resolution ultrasound was 21%~75%, of which about 4%~11% were malignant nodules. Research by Liu et al [7]. shows that the sensitivity and specificity of elastography in differentiating benign and malignant thyroid nodules are significantly higher than that of conventional two-dimensional ultrasound, VTI technology and VTIQ technology are helpful for diagnosis.

VTI elastography forms VTI images through longitudinal displacement. VTI hardness grading method classifies VTI according to gray distribution to help identify benign and malignant thyroid nodules. It will not be affected by the hardness of surrounding glands or will be less affected. The VTI area ratio method is helpful to distinguish the nature of nodules because malignant nodules show invasive growth and invade surrounding glands. The area of nodules on VTI images is larger than that on gray-scale images, while benign nodules show expansive growth. VTI elastic technology has high application value. However, the VTI hardness grading method is still limited, and the grading of VTI images is easily influenced by doctors' subjective judgment.

Zhang [8] studied the SWV value of 95 thyroid nodules, the average SWV of benign nodules was (2.11±0.53) m/s, and the average SWV of malignant nodules was (3.18±0.39) m/s , Which is similar to the results of this study. The measured value of SWV reflects not the absolute value of the hardness of the nodule, but the relative value compared with the hardness of the surrounding tissue. Therefore, the causes of misdiagnosis of benign thyroid nodules by SWV measurements are mostly due to factors such as fibrosis, hyaline degeneration and calcification in nodules, especially the increase of tissue hardness caused by calcification in nodules, and the infiltration of a large number of inflammatory cells, factors such as the release of colloid in the follicles and edema of tissue cells, which can increase tissue hardness and SWV value. Misdiagnosis of malignant lesions is due to the decrease of SWV value caused by hemorrhage and liquefaction. In addition, since most malignant nodules are thyroid papillary microcarcinoma, the nodule volume is small and the size of the sampling frame is fixed, which may cover the surrounding normal thyroid tissue during measurement, resulting in a decrease in shear wave velocity.

CEUS enhancement pattern is different in benign and malignant thyroid nodules. A large number of studies show that benign nodules are mainly annular enhancement, while malignant nodules are mainly uneven low enhancement, which is similar to the results of this study. Based on this standard, CEUS has 68.1%, 76.86%, 70.7%, 66.1% and 75.33% sensitivity, specificity, accuracy, positive predictive value and negative predictive value for diagnosing benign and malignant thyroid nodules respectively. It is consistent with Xie et al [9]. In this study, malignant nodules with a diameter of less than 10mm are mainly hypovascular in contrast, which is similar to the report by Xu et al [10] that the contrast enhancement mode of thyroid malignant nodules is closely related to the nodule size. CEUS mostly showed centripetal, uneven low enhancement, and obvious early resolution of contrast agent. ARFI showed that the SWV value and SWV ratio in malignant nodules were significantly higher than those in benign thyroid nodules, similar to the results of Wu Yijuan [11].

ARFI and CEUS have high diagnostic value for thyroid solid nodules in the study, and there is no difference between the two. However, due to certain overlap of elastic systems between different tissues and certain overlapping of enhancement features of benign and malignant thyroid nodules, ARFI and CEUS alone have certain misdiagnosis. The sensitivity and accuracy of CEUS combined with ARFI increased to 87% and 98.1%, indicating that the diagnostic accuracy of combined diagnosis of thyroid nodules is significantly improved, the misdiagnosis rate is reduced, and the diagnostic accuracy is significantly higher than that of both alone.

5. Conclusion

The combination of contrast-enhanced ultrasound and acoustic pulse radiation force imaging has high diagnostic value for benign and malignant thyroid nodules. It has high differential diagnostic value for solid thyroid nodules and TIRADS type 3 and type 4 nodules. It can improve the differential diagnostic rate,get more imaging information, and guide the clinic for targeted surgery and treatment.

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