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Original Article

Ultrasound elastography combined with thyroid imaging reporting and data system classification in differential diagnosis of benign and malignant thyroid nodules

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Abstract: Objective: This study aimed to evaluate the diagnostic value of real-time ultrasound elastography (UE) and thyroid imaging reporting and data system (TI-RADS) classification in the differentiation of benign and malignant thyroid glands. Methods: A total of 238 patients (260 cases of nodular lesions) treated in our hospital was selected. Pathological examinations were performed on the lesions (184 benign lesions, 76 malignant lesions). All nodules were assessed using UE and TI-RADS, and were differentiated into malignant and benign lesions based on the elasticity grade of UE and TI-RADS classification. The results of the two diagnostic methods were compared to evaluate the diagnostic values of UE, TI-RADS, and UE + TI-TADS in differentiating the benign and malignant nodules. The thyroid nodules were divided into two categories by a diameter of 10 mm to compare the diagnostic values of UE and TI-RADS in assessing thyroid nodules of varied diameters. Results: Comparisons among different diagnostic methods showed that the sensitivity, specificity and accuracy of UE + TI-RADS were significantly higher than those of UE or TI-RADS ($P < 0.05$). The classification of thyroid nodules based on diameters suggested that the accuracy and sensitivity of TI-RADS were significantly higher than those of UE for nodules ≤ 10 mm while the accuracy of TI-RADS was higher than that of UE for nodules > 10 mm ($P < 0.05$). Conclusion: TI-RADS can be used as a qualitative diagnostic method for thyroid nodules. The accuracy of TI-RADS in qualitative diagnosis was significantly higher than that of UE. The accuracy and sensitivity of TI-RADS were significantly higher for nodules with diameters below 10 mm. However, the combined use of UE and TI-RADS showed a better performance than either of the single methods. Therefore, the combined use of two methods is recommended to increase diagnostic accuracy.

Keywords: Thyroid, real-time ultrasound elastography, TI-RAD classification, benign and malignant, differential diagnosis

Introduction

Thyroid nodules are one of the most common diseases in the endocrine system. An epidemiological survey data indicated that in some areas of iodine deficiency, the detection rate of thyroid nodules was 3%-7% through the population. The detection rate of high-resolution ultrasound was 20%-76%. Research has found that thyroid nodules could be cancerous. In recent years, changes in lifestyles and diet have led to gradual increase in the prevalence of thyroid cancer. The increased rate of the annual prevalence has risen to the greatest among all malignant tumours [1-3].

Early diagnosis and intervention of a thyroid nodule is very important to improve the prognosis of disease. The qualitative diagnosis of thyroid nodules provides reference for the selection of subsequent treatment plans. Pathological examination is the conventional method to differentiate benign and malignant nodules. However, due to its invasiveness and poor replicability, the pathological examination is rarely used at present [4, 5]. In recent years, high-frequency transducers have been generally adopted in clinical practice. The high-frequency transducer significantly improved the resolution of ultrasound imaging. Two-dimensional ultrasound, colour Doppler ultrasound and other

detection methods have become important qualitative diagnostic methods for thyroid nodules. Real-time ultrasound elastography (UE) is a recently developed detection method. This method assesses the level of malignancy based on the stiffness of the tissue. Higher degree of stiffness indicates higher level of malignancy. Currently this technique is effective for the preoperative diagnosis of thyroid nodules [6, 7]. TI-RADS classification is a standardized diagnostic method based on margin features, borders, morphology, internal echotexture, posterior echotexture and other parameters of thyroid nodule. Studies have indicated that TI-RADS can provide reference for the quantitative assessment of the malignancy among thyroid nodules [8, 9]. This study aimed to assess the diagnostic value of UE and TI-RADS detection and classification techniques in determining the malignancy of thyroid nodules, so as to indicate a reliable method for detecting the degree of malignancy in patients with early-stage thyroid nodules.

Materials and methods

General information

A total of 238 patients (260 cases of nodular lesions) who received routine ultrasound examinations in our hospital from January 2019 to April 2020 were selected. Among the 238 patients, there were 99 males and 139 females, aged from 21 to 78 years with an average age of (51.11 ± 7.21) years. There were 120 patients with solitary nodules and 118 patients with multiple nodules. All cases were validated by pathological examination.

Inclusion criteria: (1) patients with thyroid nodules diagnosed using palpation, ultrasound examination and other methods; (2) patients with no abnormalities in thyroid functions; (3) patients who were conscious and could cooperate with the study; (4) patients with complete medical records for clinical statistical analysis; (5) this study had obtained the approval from the hospital ethics committee; (6) the patients or family members signed informed consent.

Exclusion criteria: (1) patients with mental disorders; (2) patients aged ≤ 18 years; (3) women during pregnancy or lactation; (4) patients with other malignant tumours; (5) patients with diseases affecting vital organs such as liver and kidney; (6) patients with isolated thyroid cysts; (7) patients with coagulation disorders.

Intervention method

Real-time UE and TI-RADS were both performed in the patients using Hitachi HI VISION 900, and HI Vision Preirus colour Doppler ultrasound machines with linear-array transducers at frequency of 6-13 MHz. The patient was in a supine position with hyperextension of the head to fully expose the imaged area. The machine system was set to the mode of thyroid detection. The depth and enhancement were adjusted to allow the most optimal display of the image. The greyscale mode was set first to examine the lesions at both transverse and longitudinal views to closely observe the location, size, morphology, border, internal echotexture, microcalcifications, lymph node metastasis and aspect ratios of the nodules. Elasticity imaging was then selected. The transducer was oriented perpendicular to the surface to induce microvibration at the lesions. The focal zone was set at twice the area of the lesions. The dual-mode real-time display function was used to simultaneously examine the 2D image and elasticity image to compare the hardness of the lesions and the surrounding tissues. The detection results were analysed by two experienced sonographers. If different diagnosis results were found, senior physicians were invited for consult to make a diagnosis.

Assessment parameters and evaluation standards

Classification of elasticity imaging based on stiffness: Varied colours were used to indicate the elasticity of the tissue in the elastogram. Green depicted an intermediate level of elasticity, red indicated relatively softer areas, and red depicted relatively stiffer areas. The scoring system is as following: Score 1 indicates that the whole lesion is coded in green; Score 2 indicates that 90% of the lesion is coded in green; Score 3 indicates that 50% of the lesion is coded in green; Score 4 indicates that more than 90% of the lesion is coded in blue; Score 5 indicates that the whole lesion is coded in blue. A score of 1-2 suggests the mass examined was benign while a score of 3-5 suggests the mass examined was malignant [10].

Table 1. Results of pathological examination of thyroid nodules n (%)/(x ± s)

Group	Category	Quantity (n=260)	SR value	*t*	*P*
Benign group (n=184)	Nodular goiter	101 (54.89)	2.78 ± 0.55	19.649	< 0.001
	Adenoma	50 (27.17)			
	Simple adenoma	21 (11.41)			
	Follicular adenoma	12 (6.52)			
Malignant group (n=76)	Papillary carcinoma	56 (73.68)	4.39 ± 0.71		
	Medullary carcinoma	20 (26.32)			

Thyroid TI-RADS classification: The thyroid nodules were classified into 5 categories based on TI-RADS. TI-RAD 0 indicates normal glands or diffuse hyperplastic thyroid; TI-RAD 1 indicates perinodular halos that are mainly cystic; TI-RADS 2 has mostly solid nodules with well-defined border, partially heterogeneous echotexture, and coarse calcification; TI-RADS 3 has solid and hypoechogenic mass with homogeneous echotexture and well-defined border; TI-RADS 4 has 1-2 ultrasonographic characteristics (UC) of malignancy such as microcalcification, ill-defined border, and deformed lymph nodes; TI-RADS 5 has 3 or more UC features of malignancy. In this study, TI-RADS 1-3 was used to indicate benign nodules and 4-5 to indicate malignant nodules [11].

Statistical analysis

The statistical analysis of collected data was performed using SPSS 20.0 software. The measurement data were expressed as (x ± sd) and the difference between groups was assessed using t test. The count data were expressed as [n (%)], and the difference between groups was assessed by Chi-square test. ($P < 0.05$) was considered statistically significant [12].

Results

Results of pathological examinations of thyroid nodules

The results displayed a total of 260 thyroid nodules, including 184 benign nodules with 101 thyroid goitres, 50 adenomas, 21 simple adenomas, and 12 follicular adenomas, with an average SR value of 2.78 ± 0.55, and 76 malignant nodules with 56 papillary carcinomas and 20 medullary carcinomas, with an average SR value of 4.39 ± 0.71. The difference in the SR values between the two groups was statistically significant ($P < 0.05$) (**Table 1**).

Comparison of the diagnostic value of UE technique, TI-RADS classification and UE + TI-RADS for benign and malignant thyroid nodules

The UE detected 80 malignant nodules and 180 benign modules. According to the pathological examination results, the evaluation results of UE had a sensitivity of 80.26%, specificity of 89.67%, accuracy of 86.92%, positive predictive value of 76.25%, and a negative predictive value of 91.67%.

The TI-RADS detected 81 malignant nodules and 179 benign nodules. According to the pathological examination results, the evaluation results of TI-RADS had a sensitivity of 67.11%, specificity of 83.70%, accuracy of 78.85%, positive predictive value of 62.96%, and negative predictive value of 86.03%.

The combined method of UE and TI-RADS detected 183 malignant nodules and 77 benign nodules. The evaluation results of the combined method had a sensitivity of 96.05%, specificity of 97.83%, accuracy of 97.31%, positive predictive value of 94.81%, and negative predictive value of 98.36%.

The sensitivity, specificity, accuracy, positive predictive value and negative predictive value of the combined method were much higher than those of UE and TI-RADS alone ($P < 0.05$) (**Figure 1**).

TI-RADS classification for evaluation of thyroid nodules

The ultrasonic characteristics of different thyroid nodules were compared by TI-RAD. It was found that there was significant difference in the border, margin, posterior echotexture, calcification, distribution of blood flow, growth, morphology, and tumour-draining lymph nodes between malignant and benign thyroid nodules ($P < 0.05$) (**Table 2**).

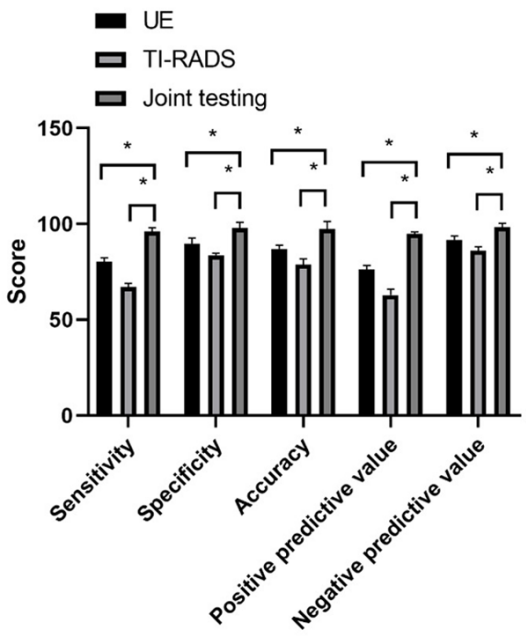

Figure 1. Comparison among the diagnostic values of the three detection methods for benign and malignant nodules. The sensitivity, specificity, accuracy, positive predictive value and negative predictive value of the combined method were much higher than those of UE and TI-RADS ($P < 0.05$).

Comparison of the diagnostic values of UE and TI-RADS for thyroid nodules with varied size

The 260 thyroid nodules were divided into two groups: one group with nodules ≤ 10 mm, the other group with nodules > 10 mm. The diagnostic values were compared between UE and TI-RADS for the qualitative analysis of benign and malignant thyroid nodules with varied diameters. The results indicated that for nodules ≤ 10 mm, the accuracy and sensitivity of TI-RADS were significantly higher than those of UE ($P < 0.05$). For nodules > 10 mm, the accuracy of TI-RADS was significantly higher than that of UE ($P < 0.05$) (**Figure 2**).

Discussion

Thyroid cancer can occur at any age, and it is one of the most common malignant tumours found in China. In recent years, changes in lifestyles and diets have led to an annual increase in the prevalence and detection rate of thyroid cancer. A thyroid nodule is a lump formed in the thyroid and it can move up and down with the thyroid when swallowing. It is a common clinical disease. Thyroid nodules have multiple causes, such as thyroid degenerative disease, inflammation, autoimmunity, and neoplasm, all of which can lead to thyroid cancer [13, 14]. High-resolution ultrasound examinations found that more than 70% of young and middle-aged population had thyroid nodules. Although most of the detected nodules were benign lesions, about 5%-10% were malignant. The common histological types of malignant thyroid nodules include papillary carcinoma, follicular carcinoma, medullary carcinoma, undifferentiated carcinoma, *etc*. In recent years, the incidence of malignant thyroid nodules has been increasing annually, and the rate of rise is the highest among all tumours. The early differentiation of malignant and benign thyroid nodules could significantly assist the clinical treatment of patients and improve the quality of lives in patients [15, 16].

Pathological examination is the conventional method to differentiate benign and malignant nodules. However, due to its invasiveness and poor replicability, the pathological examination is unpopular among patients. With the continuous development of imaging technologies, various ultrasound methods, with their convenience, non-invasiveness, and good replicability, are increasingly prominent in the differentiation of benign and malignant thyroid nodules. They are by far the most common detection methods for thyroid nodules [17]. Studies indicated that the clinical application of high-frequency transducers improved the resolution of ultrasound. The diagnostic accuracy of thyroid nodules reached 74%-82%. In addition, ultrasound examination can comprehensively evaluate various clinical features of the thyroid nodules. *The guidelines for the diagnosis of thyroid nodules and differentiated thyroid cancer, 2013* suggested that all patients with thyroid nodules should be examined with a neck ultrasound. The level of recommendation for this method was A [18].

In this study, the values of real-time UE and TI-RADS classification in the qualitative diagnosis of thyroid nodules were evaluated. TI-RADS is a reporting system of thyroid nodules established by the American College of Radiography. This method classifies the level of malignancy of thyroid nodules into scores of 0-5 according to the results of routine ultrasound examination. TI-RAD 1-2 is benign and TI-RAD 3-5 is

Table 2. The evaluation results of thyroid nodules using TI-RADS classification

General clinical data		Benign (n=184)	Malignant (n=76)	X^2	*P*
Margin	Clear	171	1	12.298	< 0.001
	Unclear	2	20		
	Blurred	11	56		
Border	Regular	176	1	15.998	< 0.001
	Irregular	5	37		
	Ill-defined	3	31		
	Spiculated	0	4		
	Angled	0	3		
Posterior echo	Enhancement	154	2	20.229	< 0.001
	Attenuation	4	64		
	No change	26	10		
Calcification	Non-calcification	90	7	22.239	< 0.001
	Microcalcification	2	61		
	Coarse calcification	92	8		
Distribution of blood flow	No blood flow	91	15	30.990	< 0.001
	Little blood flow	43	21		
	Rich blood flow	50	40		
Growth	Parallel (aspect ratio < 1)	183	46	77.621	< 0.001
	Vertical (aspect ratio ≥ 1)	1	30		
Morphology	Regular	180	10	209.402	< 0.001
	Irregular	4	66		
Draining Lymph nodes	Normal	184	6	233.775	< 0.001
	Deformed	0	70		

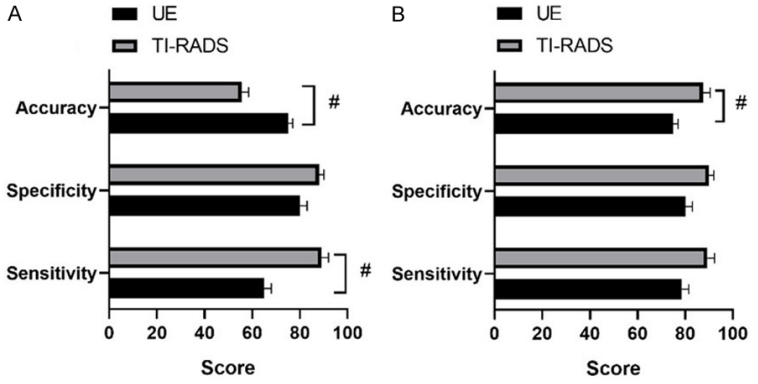

Figure 2. Comparison between the diagnostic values of UE and TI-RADS in assessing thyroid nodules of varied diameters. The accuracy and sensitivity of I-RADS were significantly higher than that of UE for nodules ≤ 10 mm. The accuracy of TI-RADS was higher than that of UE for nodules > 10 mm ($P < 0.05$). # indicates that the difference of the same index within group was statistically significant.

malignant [19]. Studies indicated that TI-RAD 1-2 mostly corresponded to nodular goitre, Hashimoto's thyroiditis and other benign nodules, and TI-RAD 4-5 mostly corresponded to papillary carcinoma, medullary carcinoma and other malignant nodules. The results of pathological examination indicated 184 benign nodules and 76 nodules out of the 260 nodules included. Based on the outcome of pathological examination, the evaluation results of TI-RADS were shown to have a sensitivity of 67.11%, specificity of 83.70%, accuracy of 78.85%, positive predictive value of 62.96%, and negative predictive value of 86.03% [20, 21]. These data are similar to the data from other studies. It implies that TI-RADS still has errors and possibilities of misdiagnosis when differentiating benign and malignant thyroid nodules. The different features of benign and malignant nodules based on TI-RADS classification were further analysed. The results showed that malignant nodules had irregular internal morphology, ill-

defined and irregular borders, posterior hypoe chogenicity, microcalcification, posterior attenuation, aspect ratio > 1, hypervascularity, and cervical lymph node swelling, which were similar to other studies. This indicates that TI-RADS has high clinical values in the evaluation of benign and malignant thyroid nodules.

UE is a qualitative diagnosis method based on the stiffness of lesions and is one of the most effective assisting methods for the preoperative diagnosis of thyroid nodules. The level of malignancy is correlated to the texture of the thyroid nodules. The benign nodules are soft and smooth. Increased stiffness of the nodule indicates increased level of malignancy. The UE technique, which is based on this property, applies a constantly changing force to the tissue and measures the degree of deformation to evaluate the stiffness of the nodule. The degree of malignancy is then assessed [22]. Studies indicated that the UE technique was clinically approved for the differential diagnosis of benign and malignant nodules in prostate, blood vessels, mammary glands, thyroid, and other superficial organs as well as identification of liver fibrosis. Compared to 2D and colour Doppler ultrasound, UE has considerable advantages in the qualitative diagnosis of thyroid nodules [23]. This study showed that the UE had a sensitivity of 80.26%, a specificity of 89.67%, an accuracy of 86.92%, a positive predictive value of 76.25%, and a negative predictive value of 91.67%, which was similar to the outcomes from other studies. This suggested that UE also had relatively high diagnostic value.

We compared the advantages and disadvantages of UE and TI-RADS in the qualitative diagnosis of thyroid nodules. The result indicated little difference in the sensitivity, specificity, accuracy, positive predictive value and negative predictive values between the two methods. However, the combined use of UE and TI-RADS has been shown to have better performance than either of the single method, suggesting that the combined method can significantly improve the diagnostic values. A study suggested high similarity between the conventional ultrasound imaging of benign and malignant thyroid nodules, which led to the difficulty in diagnosis. Although TI-RADS had high resolution and clearer ultrasound imaging compared to the conventional ultrasound, the diagnosis of grade 3 nodules was difficult due to the similarity between the ultrasonic imaging of grade 3 and that of grade 2 and 4 nodules. Therefore, the qualitative diagnosis was subjective and heavily relied on the experience of the physicians. Different physicians could make different diagnoses of the same case, leading to misdiagnosis [24]. The UE technique is a qualitative diagnostic method based on tissue stiffness. The difference in the degree of tissue deformation under the external force is used for the differentiation of benign and malignant tumours. Different colours are used to indicate the strain ratios of the tissue. A study on the differential diagnosis of 211 benign and malignant thyroid nodules indicated that the sensitivity, specificity, and accuracy of UE were 85.7%, 96.0%, and 93.0%, respectively. Further analysis indicated that 80.3% of the benign lesions had an elasticity score of 0-2, and 86.6% of the malignant lesions had an elasticity score of 3-4. The UE score of benign nodules was mainly ≤ 2, while the UE score of papillary carcinoma was mainly ≥ 3, which was similar to the results of this study [25]. The thyroid nodules were then divided into two categories based on diameters to evaluate the diagnostic values of UE and TI-RADS in assessing thyroid nodules of varied diameters. The results indicated that the accuracy and sensitivity of TI-RADS were significantly higher than those of UE for nodules ≤ 10 mm while the accuracy of TI-RADS was higher than that of UE for nodules > 10 mm. We believed that the difference in diagnostic results between TI-RADS and UE revealed that the TI-RADS had a higher resolution in the detection of microstructures and thus had a higher sensitivity in the diagnosis of micronodules. On the other head, the diagnostic results of UE were affected by the size of focal zone, depth of nodules, anatomical structures, and other factors, which could lead to false positive or false negative results [26].

In conclusion, TI-RADS could be used as a qualitative diagnostic method for thyroid nodules. The accuracy of TI-RADS in qualitative diagnosis was higher than that of UE. The accuracy and sensitivity of TI-RADS were significantly higher in nodules with diameters below 10 mm. However, the combined use of UE and TI-RADS had better performance than either of the single method. Therefore, the combined use of

two methods is recommended to increase diagnostic accuracy. The study has three limitations as following: (1) The sample size was relatively small, which led to a lack of comprehensiveness in the results. (2) The TI-RADS classification has certain limitations, thereby failing to include all cases of thyroid nodules. This leads to errors in the outcomes. (3) The pressure and frequency in the UE should be emphasized more. Hence, a follow-up study with a larger sample size and more diverse diagnostic methods is planned to provide a more detailed theoretical basis for the treatment of patients with thyroid nodules.

Disclosure of conflict of interest

None.

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