Original Article
Malignancy risk assessment of category 4 nodules by applying acoustic radiation force impulse in thyroid imaging reporting and data system

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Abstract: This study aimed to determine whether acoustic radiation force impulse (ARFI) can help to regulate thyroid imaging reporting and data system (TI-RADS) category 4 lesions and reassess the malignancy risk for a better selection of nodules submitted to fine-needle aspiration (FNA). ARFI was performed on 265 patients with 271 TI-RADS category 4 thyroid nodules. We calculated virtual touch tissue imaging (VTI) image grade, area ratio (VTIAR) and shear wave velocity (SWV) of lesions with VTI and virtual touch tissue quantification (VTQ). The categories of nodules were upgraded with higher-stiffness and downgraded with lower-stiffness, and the risks of malignancy changed accordingly. Surgical histology findings confirmed that 109 nodules were malignant and 162 nodules were benign. The cut-off values were VTI grade ≥ IV, VTIAR ≥ 1.12 and SWV ≥ 2.81 m/s, respectively. The diagnostic performance of the modified TI-RADS was statistically higher than that of TI-RADS (AUC: 0.939 vs 0.857; \( P < 0.05 \)). By limiting the sizes and malignancy risks of nodules using the modified TI-RADS, the number of benign nodules which should undergo FNA could be reduced by 62 cases. ARFI is helpful to adjust the TI-RADS classification and aid doctors in making appropriate decisions in terms of FNA recommendation.

Keywords: Thyroid nodules, acoustic radiation force impulse, thyroid imaging reporting and data system, fine-needle aspiration, elastography, ultrasound

Introduction
Thyroid nodules are detectable in 19-67% of the general population by the widely use of high-resolution ultrasound examination [1, 2], and about 5-15% of these nodules account for cancers [3, 4]. Though the incidence of thyroid cancers appears to be increasing by 4% per year [5], accurate diagnosis and appropriate treatment can significantly improve the prognosis of patients and alleviate the anxiety of the people. In recent years, some reports [6-9] have respectively proposed several different kinds of thyroid imaging reporting and data systems (TI-RADS), which are based on the suspicious ultrasound (US) signs, to develop formatted terminologies and standard models for accurate characterization of thyroid nodules and malignancy risk-stratification. Most of these systems were rarely applied because of their complexity. Among them, TI-RADS designed by Kwak et al [9] is a simple and effective process by referring to the malignancy risks from the Breast Imaging Reporting and Data System (BI-RADS) categorization. They considered that the five US suspicious features, including solid component, hypoechogenicity and marked hypoechogenicity, microlobulated or irregular margins, microcalcifications, and taller-than-wide shape, are related to malignant nodules, and defined TI-RADS as category 3 (no suspicious features), 4a (one suspicious feature), 4b (two suspicious features), 4c (three or four suspicious feature), and 5 (five suspicious features). The malignancy risks of 3 category and 5 category are namely 1.7% and 87.5%, corresponding to highly probable benign lesion and high suspicion for malignant lesion, respectively. However, category 4 nodules are generally defined as undetermined lesions and their malignancy rate is widely range from 3.3% to 72.4% (the fitted probability for malignancy, 4a:
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Figure 1. The flowchart of thyroid nodules selection and rates of malignancy.

3.6-12.7%; 4b: 6.8-37.8%; 4c: 21-91.9%) [9], resulting in the confusion of whether to recommend the patients to go through biopsy. Owing to the fact that performing fine-needle aspiration (FNA) in all category 4 lesions is not cost effective, there is a need to add additional parameters and to establish improved characterization to select suspicious nodules for invasive procedure.

In 2013, the American College of Radiology Breast Imaging and Data System (ACR BIRADS Fifth Edition, 2013) [10] developed elasticity assessment as an objective parameter, which is similar to the conventional US features, for breast lesion diagnostic. They pointed out that stiffness as a feature of malignant masses may be considered along with their morphologic characteristics. Though many studies have confirmed that the hardness is related to the nature of thyroid lesion [11, 12], it was not formally included in any previous TI-RADS or the American Thyroid Association (ATA) guideline [13].

As a novel US-based elastography technique, acoustic radiation force impulse (ARFI) performs stiffness evaluation by applying short-duration acoustic pulse transmitted from the transducer to deform the localized tissue, and tracking longitudinal small displacement and transverse shear wave transmission within the region of interest (ROI). The former is named as virtual touch tissue imaging (VTI) whereas the latter is named as virtual touch tissue quantification (VTQ) [14-16]. Previous studies [14, 17, 18] have proved that VTI and VTQ are helpful to differentiate malignant thyroid nodules from benign ones and supplement conventional US to improve the diagnostic performance in thyroid diseases. To our knowledge, however, there are few research results focusing on the combination of ARFI and TI-RADS of Kwak et al. Furthermore, the efficiency of VTI and VTQ in predicting the malignancy risk of undetermined category 4 nodules has not individually been evaluated. The aim of this study is to confirm whether ARFI images including VTI and VTQ could be used to adjust the TI-RADS criterion and improve the accuracy of category 4 malignancy risk-stratification, especially to provide more strict standards in selecting patients for FNAB.

Materials and methods

Patient

The study was approved by the Ethical Committee of the first affiliated hospital of
Harbin medical university and informed consent was obtained from all patients. From May 2012 to November 2016, 509 patients with thyroid nodule disease were scanned using the ACUSON S2000 ultrasound system (Siemens Medical Solutions, CA, USA) with a 4 to 9 MHz linear transducer and ARFI software inside. Thyroid nodules were included when they met the following inclusion standards: (i) euthyroid gland was normal; (ii) the location of nodule was in the left or right lobe, due to the fact that the isthmus of thyroid is lack of adequate glands; (iii) the largest diameters of nodules were at least 1.0 cm and less than 3.0 cm, because there should be enough thyroid tissue surrounding the nodules at the same depth to obtain a meaningful VTI picture; (iv) the volume of cystic portion or coarse calcification in nodules was less than 25% [19]; (v) nodules that had complete images of US and ARFI (including VTI and VTQ) and definite pathological results from postoperative biopsy; (vi) None invasive procedures performed on the patient before because ablation or FNAB might cause a possible US and elastic change [14].

According to TI-RADS of Kwak et al, the lesions were classified as 3, 4 and 5 categories with the agreement of 2 experienced sonographers on the conventional US. Finally, in this study, 271 thyroid nodules of TI-RADS category 4 from 265 patients (mean age 47.3±10.7 years; range, 18 to 78 years), which included 56 men and 209 women, were recruited (mean size 1.7±0.5 cm; range, 1.0 to 3.0 cm) and further divided into 4a, 4b and 4c categories. Figure 1 is a flow chart of thyroid nodules selection.

VTI image grade, VTIAR and VTQ

ARFI elastography were performed in the best two-dimensional section of the target nodules after US examination. Place the probe gently on the neck and make the patient hold breath, then switch on VTI mode, and the nodule was displayed in the center of the sampling box with adequate surrounding thyroid tissue (once to twice the size of the lesions). The VTI images and the grayscale images were simultaneously shown on the different sides of screen when the update button is pressed. There were two methods in Xu’s report [19] for VTI image evaluation. For the first one, based on the proportion of whiteness and blackness in the lesion, VTI image was divided into 6 grades as follows: grade I, almost white; grade II, predominantly white with a small amount of black; grade III, equally white and black; grade IV, predominantly black with a small amount of white; grade V, almost black with few white points; grade VI, completely black. For the other one, VTI area ratio (VTIAR) is calculated the ratio of VTI image area (A2) to ultrasound image area (A1) by the automatic identification technology, which were

Figure 2. A. Receiver operating characteristic curve (ROC) analyses of VTI image grade, VTIAR and VTQ; B. ROC analyses of TI-RADS and the modified TI-RADS classification.
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Manually revised if obvious errors observed (Figures 3B and 4B). The results of images evaluation were depended on consensus from two experienced sonographers. Higher grade and larger area ratio related to harder tissue and higher risk of malignancy nodule. In VTQ mode, the ROI (the size for VTQ is 6 mm*5 mm) was placed on the solid portion of the lesion, avoiding coarse calcification and cystic portions as far as possible to prevent measurement deviation. With the patient breath-hold and the update button performance, five measurements of shear wave velocity (SWV) which expressed in m/s were consecutively performed on random positions of the nodule. The average value of five measurements was considered as the elastic hardness of the lesion and a higher measured value indicated a harder nodule. The values were occasionally showed as XXX m/s, which were beyond the range of VTQ measurement of the transducer, we considered they are valuable and recorded as 9 m/s after excluding the following factors: patient respiration or movement, operator motion or improper pressure, inappropriate ROI placement on the liquid area or bulky calcification [14, 20].

Statistical analysis

Statistical analysis was performed by SPSS (Version 23.0, IBM, USA) and MedCalc (Version 15.6.1, MedCalc Software bvba, Belgium). Data were expressed in the mean of value ± standard deviation (SD). The receiver operator characteristic (ROC) curves were constructed to evaluate the diagnostic performance of VTI image grade, VTIAR and VTQ in differentiating...
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To distinguish malignant and benign nodules, and to obtain the sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV), respectively. The best cut off value for each ARFI parameter was optimized when Youden index (YI) was maximum (sensitivity + specificity -1). Z-test was adopted to compare the areas under the ROC curve (AUC) for evaluating the diagnostic performance of VTI image grade, VTIAR and VTQ. Final pathological diagnosis was used as the gold standard. Any p values < 0.05 were considered statistically significant.

We also compared the diagnostic value of TI-RADS category and a modified TI-RADS category for TI-RADS +VTI image grade+ VTIAR+ VTQ, which represented the combination of TI-RADS and ARFI. The modified TI-RADS category adjusted the category of thyroid nodule based on the following standard: when VTI image grade or both VTIAR was greater than or equal to the cut-off value (VTI positive), and VTQ was greater than or equal to the cut-off value simultaneously (VTQ positive), the category of nodule rose one level; when VTI image grade, VTIAR and VTQ were less than the cut-off value at the same time, the category of nodule dropped one level; TI-RADS grade for the nodule remain unchanged in any condition besides the mentioned criterions above.

Results

Pathology diagnoses

Of the 271 thyroid nodules with postoperative pathological diagnosis, 109 were malignant...
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Among 109 malignant lesions, there were 108 cases with papillary carcinoma and 1 case with medullary thyroid carcinoma. The 162 benign lesions included 125 nodular goiters, 29 follicular adenomas, 6 Hashimoto's nodules and 2 subacute granulomatous thyroiditis. The basic characteristics of the patients and the nodules are shown in Table 1.

**VTI image grade, VTIAR and VTQ**

TI-RADS and ARFI features of malignant and benign thyroid nodules are presented in Table 1. Besides the index of composition, there were significant differences in TI-RADS features between benign nodules and cancers ($p < 0.05$). VTI grade IV to VI was usually found in malignant whereas grade I to III was generally found in benign nodules ($p < 0.05$). The area ratio and VTQ value of malignant nodules were statistically higher than that of benign nodules (means ± SD, VTIAR: 1.22±0.20 vs 1.03±0.19; VTQ: 5.05±2.49 vs 2.27±1.19; all $p$ value $< 0.05$) (Figures 3 and 4). The best cut-off values of VTI grade, VTIAR, VTQ were grade ≥ IV, AR ≥ 1.12 and SWV ≥ 2.81 m/s, respectively (Figure 2A). The sensitivity, specificity, accuracy, PPV,
NPV, YI, AUC and 95% confidence interval (95% CI) of two methods are shown in Table 2. All of the nodules divided to 4a, 4b and 4c based on the TI-RADS categorization were compared with pathological results to calculate the risk of malignancy in different grades. Then the modified TI-RADS category changed the nodules’ classification and risk. All of the results are shown in Table 3.

Based on thyroid nodule diagnostic FNA guidance of ATA [13] (Table 4), all of the nodules were divided into three groups according to the largest dimension (d) as follows: group 1, 1.0 cm ≤ d < 1.5 cm, 119 nodules; group 2, 1.5 cm ≤ d < 2.0 cm, 83 nodules; group 3, d ≥ 2.0 cm, 69 nodules. The number of nodules, which should undergo FNA due to the risk of malig-
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Table 5. The change of categories and numbers of thyroid nodules recommended for FNA based on risk of malignancy by TI-RADS and the modified TI-RADS classification

<table>
<thead>
<tr>
<th>Largest dimension of thyroid nodules</th>
<th>TI-RADS categories*</th>
<th>Number of cases</th>
<th>Histopathology</th>
<th>The modified TI-RADS categories†</th>
<th>Numbers of cases</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Malignant</td>
<td></td>
<td>Malignant</td>
<td>Benign</td>
</tr>
<tr>
<td>1.0 cm ≤ d &lt; 1.5 cm</td>
<td>4b; 4c</td>
<td>96</td>
<td>52</td>
<td>44</td>
<td>4c; 5</td>
<td>60</td>
</tr>
<tr>
<td>1.5 cm ≤ d &lt; 2.0 cm</td>
<td>4b; 4c</td>
<td>65</td>
<td>32</td>
<td>33</td>
<td>4b; 4c; 5</td>
<td>52</td>
</tr>
<tr>
<td>d ≥ 2.0 cm</td>
<td>4a; 4b; 4c</td>
<td>69</td>
<td>24</td>
<td>45</td>
<td>4a; 4b; 4c; 5</td>
<td>53</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>230</td>
<td>108</td>
<td>122</td>
<td>165</td>
<td>105</td>
</tr>
</tbody>
</table>

TI-RADS = thyroid imaging reporting and data system; d = largest dimension of thyroid nodules. *The categories of nodules recommended for FNA based on risk of malignancy by TI-RADS. †The categories of nodules recommended for FNA based on risk of malignancy by the modified TI-RADS classification.

Discussion

Compared to benign nodules, thyroid cancers generally have some histopathological changes, such as papillary or follicular structures, psammoma bodies, extensive fibrosis and solid cells, which could increase the stiffness of tissue [21]. Therefore, in a VTI image, the shade of a malignant lesion is darker than that of a benign lesion and its surrounding tissue (Figures 3B and 4B), and, in the VTQ image, the stiffer the tissue is, the faster the shear wave disseminates (Figures 3C and 4C). In this study, VTI image grading and VTQ demonstrated satisfied and similar diagnostic performances in differentiating the nature of thyroid nodules. The area ratio, as a new evaluation parameter of VTI, is based on the aggressive and infiltrative growth pattern of thyroid cancer [22, 23]. The invasion and infiltration to adjacent tissue may lead to increased stiffness of the area around the tumor, thus, the visible area of the nodule on VTI image is larger than that on two-dimensional sonography. Xu et al [19] confirmed that VTIAR is a feasible method by analyzing the satisfactory results of intraobserver and interobserver agreement, and they found that the sensitivity and specificity of VTIAR were accordingly 81.4% and 87.1%, when using 1.09 as the cutoff value in another research [23]. In our study, VTIAR also showed fine diagnostic performance for predicting malignancy. In short, VTI estimates the elasticity of the whole lesion by qualitative (VTI grading) and semi-quantitative (VTIAR) methods with the adjustable sampling box, quite to the contrary, VTQ allows quantification measurement of tissue elasticity in a selected region in a lesion, and the size of ROI is fixed. Therefore, ARFI elastography, with the complementation of three parameters, is more reproducible and dependable than conventional strain elastography [24, 25].

Distinguished from simple combination of ultrasound and elastography reported in previous studies [14, 26], we built the modified TI-RADS with taking into consideration the importance and dominance of conventional US. For this reason, the grades of category 4 thyroid nodules just could be adjusted when VTI (VTI image grade or both VTIAR) and VTQ were positive or negative simultaneously. When combined with ARFI, it could obviously enhance the diagnostic performance of TI-RADS. TI-RADS 4a nodules that were downgraded to 3 category were all benign. TI-RADS 4c nodules that were upgraded to 5 category were 65 malignant and 7 benign, and the risk of malignancy rose from 75.2% to 90.3%. 12 benign lesions rose one level, which implied that both VTI and VTQ affirmed the tissues were stiff, and at the same time, 3 malignant lesions descended one grade because of soft tissues and non-aggressivity, which were diagnosed by VTI and VTQ. These phenomena are likely to be explained that the pathological features of nodules may have influenced the results of ARFI analysis. With histopathologic analysis, the interstitial components of these benign lesions showed fibroplasias in different degrees or lymphocyte infiltration, which resulted in the hardness of the tissue increased and false-positive results [21, 27, 28]. Some malignant nodules, especially microcarcinoma, are often accompanied by nodular goiter. Due to the circumambience of benign tissue, stiffness region is small in comparison and the feature of aggressive growth pattern is not really obvious. In addition, rapid growth of malignant nodules may result in inter-
nal bleeding and necrosis, which reduce the hardness of tissue. These main factors are responsible for misdiagnosis of elasticity examination. In addition, discrepancy between VTI and VTQ analysis were found in 27.8% (30/108) malignant cases and 27.8% (45/162) benign cases, whose grades were unaltered. Therefore, in our study, much more important conventional US characteristics were used along with various elasticity parameters to evaluate TI-RADS category 4 nodules, which could weaken the deviation and defects of elastography. Our study also demonstrated some consistency of two evaluation methods in every category. The risks of malignancy from kwak TI-RADS were basically compatible with our results from the modified TI-RADS classification.

Thyroid nodule diagnostic FNA is recommended for suspicious lesions with different size and malignancy risks in ATA (Table 4). In our study, the modified TI-RADS classification changed the categories of 43 nodules from the original 4a grade (the risk of malignancy, 1.6%) to 3 grade (the risk of malignancy, 0%), which meant that invasive biopsies could have been avoided in 15.9% of cases. The nodules were divided into three groups by sizes. When the malignancy risk of lesions were assessed by using TI-RADS and modified TI-RADS classification, in group 1 (1.0 cm ≤ d < 1.5 cm), group 2 (1.5 cm ≤ d < 2.0 cm) and group 3 (d ≥ 2.0 cm), the number of nodules that should be recommended for FNA were reduced from 96 to 60, 65 to 52 and 69 to 53, with the false-positive rate changing from 45.8% to 18.3%, 50.8% to 38.5% and 65.2% to 54.7%, individually. As a consequence, we considered that the use of the modified TI-RADS classification could improve the selection criterion and reduce unnecessary biopsies for TI-RADS category 4 masses. Moreover, if we aspirate the tissue which were shown hard in ARFI images, false-negative rate of FNA might be decreased. However, three malignant nodules in group 1 were not recommended for FNA by the evaluation of the modified TI-RADS classification. Consequently, closely observation of nodular size changes is necessary so that to carry out treatment timely.

This study still had several limitations. Firstly, according to ATA guideline, nodules bigger than 1.0 cm have a greater potential to be clinically significant cancers [13]. So we had not discussed small lesions in this study. Larger studies with longer follow-up are needed to carry out. Secondly, selection bias exists because of the restriction from elastography technology. Thirdly, the histologic types of malignant nodules in our study were simple that almost all were papillary carcinomas. Only one case was medullary carcinoma, and was misdiagnosed by both VTI image grade and VTQ. Until now, there was no systematic study focused on the TI-RADS and ARFI analysis of all kinds of thyroid cancer. Finally, further research about the impact of diffuse thyroid disease on TI-RADS and ARFI of nodules maybe needed.

In conclusion, our results demonstrate that ARFI is helpful in differentiating benign and malignant thyroid nodules. The modified TI-RADS classification combined conventional US and ARFI is a useful diagnosis tool for further evaluating category 4 thyroid lesions and malignancy risk-stratification. And in particular, it restricts the number of patients recommended for FNA.

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Disclosure of conflict of interest

None.

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