Differential Diagnosis of Small Single Solid Thyroid Nodules using Real-time Ultrasound Elastography

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Introduction
The prevalence of papillary thyroid microcarcinomas (PTMCs) in the general population without thyroid disease is reported to be high (3 – 36% according to autopsy studies).1 Most PTMCs show an asymptomatic course. The detection rate of smaller thyroid nodules can be increased using high-resolution ultrasonography, although it is very difficult to differentiate benign from malignant nodules at the early stage.2 Palpation is the most frequently used screening method for detecting thyroid tumours. One of the key features of assessing thyroid cancer by palpation is the degree of firmness: malignant lesions tend to be much harder than benign ones.3 Palpation is a highly subjective method, being dependent on the size and location of the nodule, and on the skill of the practitioner.4 Fine-needle aspiration biopsy has proved to be an efficient tool for the diagnosis of thyroid cancer but, despite the advantages of fine-needle aspiration biopsy, it is an invasive procedure and subject to uncertainties due to sampling and analysis.5

Real-time ultrasound elastography (USE) is a newly developed dynamic technique
that reflects the deformation or distortion of tissue in response to the application of an external quasistatic compression load. Elastography combines the detection advantages of high-frequency ultrasound with cancer diagnostic information. The real-time display presents a near-instantaneous colour ‘elastogram’ superimposed on the B-mode image. On the elastogram, different colour modes imply different tissue stiffness, thereby offering more information with respect to differentiation between benign and malignant lesions.

Rago et al. reported that B-mode ultrasound and colour Doppler ultrasound were highly predictive of malignancy only if multiple patterns were simultaneously present in a thyroid nodule. The predictive value of ultrasound increased at the expense of its sensitivity, and malignancy was predicted with high specificity by thyroid ultrasound in < 20% of patients. The sonogram was poorly differentiated for a single solid thyroid nodule < 10 mm in maximum diameter observed incidentally on physical examination without clinical symptoms.

The aim of the present study was to determine the efficacy of USE to diagnose thyroid nodules in order to detect carcinomas at a very early stage to allow for timely treatment and to improve prognosis.

Patients and methods

PATIENTS

Patients with a single solid thyroid nodule who were referred for surgical treatment to the Department of Ultrasound in Medicine, The Sixth People’s Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, China, between January and August 2009 were enrolled sequentially into the study. The inclusion criterion was a single solid thyroid nodule < 10 mm in maximum diameter with an indeterminate result from B-mode and colour Doppler ultrasonography. The exclusion criterion was post-operative anatomical abnormality of the neck.

The study protocol was approved by the Institutional Ethics Committee of The Sixth People's Hospital Affiliated to Shanghai Jiao Tong University. Written informed consent was obtained from all patients who participated.

PATHOLOGICAL DIAGNOSIS

All thyroid tumour samples were fixed in 10% formalin and embedded in paraffin blocks. Tissue sections were cut and stained with haematoxylin and eosin. The stained sections were analysed by one experienced pathologist blinded to the study’s ultrasonographic results.

EQUIPMENT

Conventional ultrasonographic and real-time USE examinations were carried out using a Hitachi EUB 8500 instrument (Hitachi Medical Systems, Tokyo, Japan) with a 4 – 9 MHz linear probe. For elastography, the system employed dedicated software (combined autocorrelation method [CAM]; Hitachi Medical Systems). This software used a complex algorithm that could process all data coming from the lesion as radiofrequency impulses. It could also minimize artefacts due to lateral dislocation, allowing accurate measurement of the degree of tissue distortion.

CONVENTIONAL ULTRASOUND IMAGING

The patient was positioned on his or her back with the neck slightly extended over a pillow. Conventional B-mode ultrasound images of the thyroid nodules were initially
obtained. The diagnostic parameters were size, shape, borders, internal echo, calcification, rear-echo change and the halo ring of the tumour. Colour Doppler ultrasound was carried out in all patients to evaluate the vascularity of the thyroid lesion. Three types of vascularity were identified: II (perinodular blood flow); IIIa (intranodular blood flow); and IIIb (perinodular and intranodular blood flow).15

REAL-TIME ULTRASOUND ELASTOGRAPHY
After conventional ultrasound examination, a longitudinal sectional elastographic examination was performed. The region of interest used for obtaining elasticity images was set to include sufficient surrounding thyroid tissue. The real-time elastogram and the grey-scale ultrasound image were displayed simultaneously in dual mode. The echo signals acquired by using the ultrasound scanner were captured by the computer of the machine and used to calculate tissue strain with the CAM. Using a freehand technique, the examiner applied a slight, constant vertical compression so the pressure indication on the screen read 3 or 4. With the use of the pressure indicator, optimal elastograms based on uniform tissue compressions were achieved. The entire elastographic examination lasted on average 8 – 10 min.16 Elastography was carried out by one radiologist with > 3 years’ experience in evaluating thyroid disorders using ultrasound. Elastograms were recorded and successively analysed by one ultrasonographer skilled in evaluating thyroid disorders and elastographic examinations and who did not know the elastogram evaluation made by the radiologist. The radiologist and the ultrasonographer agreed on the elasticity scores in > 90% of the examinations. In the remaining cases, images were simultaneously re-examined by the same two specialists.

The resultant elastogram was displayed over the B-mode image and assessed using a colour scale: green indicated ‘medium stiffness’ of the tissue, blue indicated ‘hard tissue’ and red indicated ‘soft tissue’. To classify elasticity images, the colour pattern of the thyroid lesion relative to the surrounding tissue was evaluated. The ultrasound elastographic image was classified using the Ueno and Ito elasticity score.17 A real-time USE score of 1 was assigned to nodules with elasticity in the entire examined area; a score of 2 was assigned to nodules with elasticity in a large portion of the examined area; a score of 3 was assigned to nodules with elasticity only at the peripheral part of the examined area; a score of 4 was assigned to nodules with no elasticity of the examined area (Fig. 1); and a score of 5 was assigned to nodules with no elasticity of the examined area and in the posterior shadowing (Fig. 2).

STATISTICAL ANALYSIS
Statistical analyses were carried out using the SPSS® statistical package, version 12.0 (SPSS Inc., Chicago, IL, USA) for Windows®. The ultrasonographic results obtained in the different groups of subjects were compared using the $\chi^2$-test. For all tests, $P < 0.05$ was considered to be statistically significant and $P < 0.001$ was considered to show a highly significant difference between the groups.

Results
PATHOLOGICAL FINDINGS
Fifty-one patients (38 females and 13 males; mean ± SD age 48.6 ± 10.5 years; age range 21 – 77 years) with a single solid thyroid nodule were included in this study. The mean ± SD diameter of the nodules was 8.96 ± 0.92 mm (range 3 – 10 mm). Of the 51
FIGURE 1: Papillary thyroid microcarcinoma in a 46-year old female with an irregular margin and microcalcification on the sonogram (right side) and a real-time ultrasound elasticity score of 4 on the elastogram (left side); i.e. a nodule with no elasticity of the examined area.

FIGURE 2: Papillary thyroid microcarcinoma in a 52-year old female with an irregular margin on the sonogram (right side) and a real-time ultrasound elasticity score of 5 on the elastogram (left side); i.e. a nodule with no elasticity of the examined area and in the posterior shadowing.
cases, 32 (63%) had a final diagnosis of malignancy based on histological evidence of papillary thyroid microcarcinomas. Nineteen of the 51 lesions (37%) were diagnosed as follicular adenomas.

### CONVENTIONAL ULTRASOUND

All 51 PTMC nodules were hypoechogenic on conventional ultrasound. Twenty-six nodules had microcalcifications (two with source calcification), 35 had an irregular margin, 18 were classified as colour Doppler type II and 25 were colour Doppler type III. The conventional ultrasound had an overall sensitivity of 75.00%, a specificity of 52.17% and an accuracy of 64.71%. The overall positive and negative predictive values were 65.63% and 63.16%, respectively. Microcalcifications (sensitivity 65.63%; specificity 73.68%; \(P < 0.0001\)), irregular margin (sensitivity 75.00%; specificity 42.11%; \(P = 0.052\), hence just failing to reach statistical significance) and intranodular blood flow (sensitivity 78.13%; specificity 47.37%; not statistically significant) were the ultrasound patterns that were the most predictive of malignancy (Table 1).

Twenty-eight thyroid nodules were located in the right leaf of the thyroid gland, 21 were located in the left leaf of the thyroid gland, and two thyroid nodules were located on the isthmic portion of the thyroid.

### REAL-TIME ULTRASOUND ELASTOGRAPHY

The following elasticity scores were recorded when real-time USE was performed: a real-time USE score of 1 was found in five cases (all benign lesions); a score of 2 was found in seven cases (all benign); a score of 3 was found in eight cases (five benign and three malignant); a score of 4 was found in 26 cases (two benign and 24 malignant); and a score of 5 was found in five cases (all malignant). An elasticity score of 4 – 5 was, therefore, highly predictive of malignancy (\(P < 0.0001\)), having a sensitivity of 90.63%, a specificity of 89.47%

### TABLE 1:

<table>
<thead>
<tr>
<th></th>
<th>Benign n = 19</th>
<th>Malignant n = 32</th>
<th>Statistical significance</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irregular margin on conventional ultrasound</td>
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<tr>
<td>Present</td>
<td>11</td>
<td>24</td>
<td>(P = 0.052) (NS)</td>
<td>75.00</td>
<td>42.11</td>
<td>62.75</td>
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<tr>
<td>Absent</td>
<td>8</td>
<td>8</td>
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<td>Microcalcifications on conventional ultrasound</td>
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<tr>
<td>Present</td>
<td>5</td>
<td>21</td>
<td>(P &lt; 0.0001)</td>
<td>65.63</td>
<td>73.68</td>
<td>68.63</td>
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<tr>
<td>Absent</td>
<td>14</td>
<td>11</td>
<td></td>
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<tr>
<td>Intranodular blood flow on conventional ultrasound</td>
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<tr>
<td>Present</td>
<td>10</td>
<td>25</td>
<td>NS</td>
<td>78.13</td>
<td>47.37</td>
<td>66.67</td>
</tr>
<tr>
<td>Absent</td>
<td>9</td>
<td>7</td>
<td></td>
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<tr>
<td>Real-time USE scores of 1 – 3</td>
<td>17</td>
<td>3</td>
<td>(P &lt; 0.0001)</td>
<td>90.63</td>
<td>89.47</td>
<td>90.20</td>
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<tr>
<td>Real-time USE scores of 4 – 5</td>
<td>2</td>
<td>29</td>
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NS, not statistically significant (\(P > 0.05\)).
and an accuracy of 90.20% (Table 1). The positive and negative predictive values were 93.55% and 85.00%, respectively.

Two false-positive results were observed using real-time USE; histopathological results indicated follicular adenomas with calcification. These nodules were very stiff because of their calcifications; they gave a deep blue elastographic pattern that would otherwise be characteristic of thyroid cancer. Three false-negative cases were also observed; two nodules were located on the isthmic portion of the thyroid gland.

Discussion
The detection rate of thyroid nodules is increasing with the increasing use of high-resolution ultrasonography of the thyroid gland and increasing numbers of physical examinations.18 Most of these nodules are small in the early period of thyroid disease and patients are asymptomatic. The differential diagnosis for these nodules is directly affected by the management approach, i.e. which nodules should be followed up and which should be excised. Malignant thyroid nodules < 10 mm in maximum diameter do not exhibit obvious changes in morphology, which is a problem if using conventional ultrasound for aiding diagnosis. The present study showed that conventional ultrasound diagnosed PTMCs with a sensitivity of 75.00%, a specificity of 52.17% and an accuracy of 64.71%.

Real-time USE is a newly-developed dynamic technique that evaluates the degree of distortion of a tissue under application of an external force. It is based upon the principle that the softer parts of tissues deform more readily than the harder parts under compression, thereby allowing objective determination of tissue consistency.6,7 Real-time USE was implemented for 51 nodules < 10 mm in maximum diameter with an indeterminate result on conventional ultrasound. An elasticity score of 4–5 was highly predictive of malignancy (P < 0.0001), with a sensitivity of 90.63%, a specificity of 89.47% and an accuracy of 90.20%. The stiffness of malignant thyroid tumours is harder than benign tumours because thyroid follicular adenomas comprise many follicles.19 These contain abundant pectin, which renders tissue slightly softer in comparison with papillary thyroid carcinomas, which comprise abundant fibrous vascular mesenchyma in the centre with calcified bodies.20 Real-time USE was useful in the differential diagnosis of these smaller nodules, and could assist in the detection of PTMCs.

The number of false-positive and false-negative results during real-time USE must also be considered. Two false-positive results were observed in the present study; histopathological results indicated follicular adenomas with calcification. These nodules were very stiff because of their calcifications; they gave a deep blue elastographic pattern that would otherwise be characteristic of thyroid cancer. Elastography could reflect the content of tissue stiffness, but USE did not provide useful information for benign lesions with coarse calcification.

The location of small thyroid nodules also influenced the elastographic results. In three false-negative cases, two nodules were located on the isthmic portion of the thyroid gland. Elastography could not accurately compare the degree of distortion of a tissue between the lesion and the surrounding normal tissue under compression. Real-time USE measurements did not give reliable results in this situation.

In conclusion, real-time USE is a promising imaging technique that could assist in the differential diagnosis of single
solid thyroid nodules < 10 mm in maximum diameter that give indeterminate results on conventional ultrasound. Real-time USE enhances the diagnostic confidence of ultrasonographers and has more practical utility in the differential diagnosis of PTMCs. Further studies will be necessary to confirm the results of the present study and to establish the diagnostic accuracy of this technique.

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

References

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