Differentiation of Benign From Malignant Thyroid Lesions
Calculation of the Strain Ratio on Thyroid Sonoelastography

Ping Xing, MD, Linfeng Wu, MD, Chunmei Zhang, MD, Shu Li, MD, Chunbo Liu, MD, Changjun Wu, MD

Objectives—Initial data suggest that elastography can improve the specificity of sonography for differentiating benign and malignant thyroid lesions. The primary objective of this study was to compare quantitative sonoelastography to conventional qualitative sonoelastography and sonography for thyroid nodule characterization.

Methods—Ninety-eight thyroid masses (53 benign and 45 malignant) were examined with conventional sonography and sonoelastography. The images were classified into 4 patterns according to a previously proposed classification. In addition, strain ratios of thyroid tissue to the nodule were calculated. Receiver operating characteristic curve analysis was used to compare the diagnostic performance of the strain ratio and that of conventional sonography. The final diagnosis was obtained from histologic findings.

Results—When a cutoff point of 3.79 was introduced, significantly different strain ratios for benign (mean ± SD, 2.97 ± 4.35) and malignant (11.59 ± 10.32) lesions was obtained (P < .0001). The strain ratio measurement had 97.8% sensitivity and 85.7% specificity. The area under the curve for the strain ratio was 0.92, whereas that for the 4-point scoring system was 0.85. Of the conventional sonographic patterns, microcalcification had the highest area under the curve, at 0.72.

Conclusions—Strain ratio measurement of thyroid lesions is a fast standardized method for analyzing stiffness inside examined areas. Used as an additional tool with B-mode sonography, it helps increase the diagnostic performance of the examination.

Key Words—elastography; sonography; strain ratio; thyroid lesions

In recent times, the number of people with thyroid nodules has increased steadily. Most nodules are benign, with less than 5% are malignant.1–3 Sonography is very useful for detecting thyroid nodules, but it is not very accurate in differentiating between benign and malignant tumors. Several sonographic patterns are useful for predicting thyroid malignancy, including hypoechochogenicity of the nodule, blurred or spicular margins, spot microcalcification, an anteroposterior/transverse diameter ratio of 1 or greater, and intranodular vascularity. However, none of these patterns have high sensitivity and specificity.4–6

Elastography is one of the latest technologies that can be applied to sonography for reconstructing tissue elasticity.7,8 The principle of elastography states that tissue compression causes deformation within the tissue; the displacement is smaller in harder tissues than in softer tissues. Calculation of tissue elasticity is done using real-time sonoelastography.
Sonoelastography superimposes information in color on B-mode images. Each color represents a certain level of elasticity. Blue is hard; red is soft; and green is median. This method is limited by a lack of standardization. To date, several studies have been published on the topic of applying sonoelastography to diagnose thyroid nodules. The indicated specificity and sensitivity of the method varied sharply in those studies.\(^9\)-\(^{12}\) Sonoelastography also permits calculation of tissue elasticity in real time, which, similarly to color, represents different elasticity. Elastic properties can be described quantitatively by calculating strain ratios. To fulfill this objective, we conducted a prospective study to investigate whether calculation of strain ratios also improves the differentiation of thyroid lesions. This was done by comparing strain ratios with B-mode sonography and conventional sonoelastography.

**Materials and Methods**

**Patients**

From September 2009 to 2010, we examined 91 consecutive patients who had been referred to our department for surgical treatment. The inclusion criterion was the presence of single or multiple thyroid nodules whose size did not exceed 40 mm; cystic nodules, complex and partially cystic lesions, and nodules with a calcified shell were excluded. All patients underwent surgery with subsequent histologic examination of the resected thyroid tissue. Cases with histologic findings of chronic inflammation were also excluded. Ethical approval for this study was granted by the Medical Research Ethics Committee of our university, and consent was obtained from all the patients through a common notification circular.

**Conventional Thyroid Sonography and Sonoelastography**

Conventional thyroid sonography and sonoelastography were performed using a UV-900 ultrasound system (Hitachi Medical Corp, Tokyo, Japan) fitted with a 10-MHz linear transducer. At first, conventional sonography was performed on each nodule. The presence or absence of hypoechogenicity, microcalcification, blurred margins, an anteroposterior/transverse diameter ratio of 1 or greater, and a type 3 Doppler color flow pattern\(^4\)\(^{,13}\) of the thyroid nodules was determined.

Sonoelastographic measurements were performed immediately after conventional sonography. All study participants were required to hold their breath and avoid swallowing during the course of scanning to keep the image stable. The probe was placed on the neck with light pressure, and a box was highlighted by the operator to include the nodule. Thus, an in-depth examination of the thyroid tissue was conducted. The device shows a numeric quality scale ranging from 1 to 5 to evaluate examination quality. A value of 2 or 3 was required to enable a good evaluation. The elastogram was displayed over the B-mode image in a color scale ranging from red, indicating components with the greatest elastic strain (ie, softest components), to blue, indicating components with no strain (ie, hardest components). According to the classification proposed by Rubaltelli et al,\(^9\) the visualization patterns of the nodules on the elastograms were classified into 4 types (Table 1). Patterns 3 and 4 were assumed to be characteristic findings of malignancy.

In addition, the mean strain index of the thyroid nodule and that of the surrounding thyroid tissue were measured; as far as possible, the surrounding tissue was selected as a reference at the same depth as the nodule. The average strain of the lesion was determined by selecting a representative region of interest from lesion, which was expressed as A. Then we selected a corresponding region of interest of adjacent thyroid tissue, and the average strain was expressed as B. The resultant strain ratio was calculated according to the following equation: strain ratio = \(B/A\), which reflected the stiffness of the lesion. A strain ratio of greater than 3.79 was set as the predictor of nodule malignancy. This cutoff point was decided by a receiver operating characteristic (ROC) curve so that sum of sensitivity and specificity was maximized. Each lesion was examined by 2 different physician radiologists: 1 with 6 years of experience with sonoelastography and the other with 15 years of experience with thyroid sonography and 2 years of experience with sonoelastography. The examiners were blinded to the results of other studies and histologic findings. They evaluated the elastographic findings of the lesions together, with final conclusions reached by consensus.

**Histopathologic Diagnosis**

Hematoxylin-eosin was used for staining formalin-fixed, paraffin-embedded tumor tissue as well as normal parenchyma obtained from the contralateral thyroid lobe of

<table>
<thead>
<tr>
<th>Table 1. Elasticity Scores</th>
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<tr>
<td><strong>Score</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
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<td>3</td>
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<td>4</td>
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</table>
Statistical Analysis

Statistical analysis was conducted using SAS version 9.2 for Windows software (SAS Institute Inc, Cary, NC). Data were expressed as mean ± SD. Receiver operating characteristic curve analysis was performed to assess the diagnostic value of conventional sonography, conventional sonoelastography, and strain ratios. The ROC curves were used to determine the diagnostic sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV); then the strain ratio cutoff values were optimized. A t test was performed to determine whether the strain ratios were different between the two groups. The ability of sonography and sonoelastography to independently differentiate benign from malignant nodules was analyzed by a binary logistic regression technique. In this case, the final histopathologic diagnosis was used as the reference standard. P < .05 was considered statistically significant.

Results

A total of 103 thyroid nodules were examined in this prospective study. Five nodules with histologic findings of chronic inflammation were excluded, leaving 98 nodules that were eventually included; 12 patients had 2 nodules. The mean age of the examined patients (15 men and 71 women) was 47 ± 11 years (range, 25–75 years). The examined dominant nodules had a mean size of 13.3 ± 6.8mm (range, 7–35 mm). Histologic examination indicated 45 malignant nodules (44 papillary thyroid carcinomas and 1 lymphoma) and 53 benign nodules (41 hyperplastic nodules, 9 follicular adenomas, 2 subacute thyroiditis, and 1 atypical adenoma).

Conventional Sonography

The sonographic patterns indicating malignancy included nodule hypoechogenicity (sensitivity, 71.1%; specificity, 66.0%; P = .0004), spot microcalcification (sensitivity, 51.1%; specificity, 92.4%; P < .0001), speculated margins (sensitivity, 64.4%; specificity, 86.7%; P < .0001), and an anteroposterior/transverse diameter ratio of 1 or greater (sensitivity, 62.2%; specificity, 75.4%; P = .0003). The pattern of single intranodular blood flow could not predict malignancy (sensitivity, 57.7%; specificity, 30.1%; P = .21). Of the conventional sonographic patterns, microcalcification had the highest area under the curve (AUC), at 0.72 (Table 2).

Sonoelastography

Forty-three of the 53 benign nodules had a score of 1 or 2, whereas 40 of the 45 malignant nodules had a score of 3 or 4, with sensitivity of 88.8%, specificity of 81.1%, a PPV of 80.0%, and an NPV of 89.5% (Table 3). Using ROC analysis, the AUC for this method was 0.85 (Figure 1A).

With the surrounding thyroid tissue at the same depth as a reference, the mean strain ratio for the benign lesions was 2.97 ± 4.35 (Figure 2), and the mean ratio for the malignant lesions was 11.59 ± 10.32 (Figure 3). There were significant differences between the strain ratios for benign and malignant lesions (P < .01). Figure 1B shows the ROC curve for the strain ratio assessment method used for differentiating malignant from benign lesions (for lesions <1 and >1 cm). The AUC was 0.92, and the best cutoff value was 3.79. Using the best cutoff point, the sensitivity, specificity, PPV, and NPV were 97.8%, 85.7%, 88.0%, and 97.8%, respectively.

Using the ROC analysis, the best cutoff value obtained using strain ratio assessment of the lesions in the small group (10 mm) was 4.21, and the value for the large group (>10 mm) was 3.98 (Table 4). The AUC for strain ratio assessment of the small group was 0.89 (Figure 4A), and the ratio of the large group was 0.94 (Figure 4B). Table 3 shows a comparison of the two methods in terms of the sensitivity, specificity, PPV, and NPV.

| Table 2. Areas Under the Receiver Operating Characteristic Curves for Different Features of Conventional Sonography, the 4-Point Scoring System, and the Strain Ratio |
|-----------------|---------------|-----------------|---------------|-----------------|-----------------|-----------------|
| Lesions         | Hypoechochogenicity | Microcalcifications | Speculated Margins | A/T ≥1 | Intranodular Blood Flow | 4-Point Scoring System | Strain Ratio |
| All             | 0.69           | 0.72           | 0.66           | 0.69 | 0.56 | 0.85 | 0.92 |
| ≤1 cm           | 0.62           | 0.72           | 0.65           | 0.79 | 0.53 | 0.78 | 0.89 |
| >1 cm           | 0.74           | 0.69           | 0.69           | 0.55 | 0.57 | 0.90 | 0.94 |

A/T indicates anteroposterior/transverse diameter ratio.
Sonoelastography is a new procedure that measures tissue elasticity by distorting the tissue structures using external pressure. Because softer parts of tissue deform more readily than stiffer parts, this technique enables objective evaluation of tissue stiffness from deformation rates. Currently, this tissue distortion can be displayed directly in terms of a color-coded overlay on a B-mode image (Figure 1).

To date, the most important applications of elastography included examining breast nodes.\(^{14,15}\) Sonoelastography of the thyroid is a new procedure. In all previous investigations, the elastograms were divided by the respective examiners into 4 to 6 groups according to their specific color patterns.\(^{9–12}\) On the basis of our preliminary experience, we chose the 4 color patterns proposed by Rubaltelli et al\(^9\) as a reference.

In our study, 40 of 44 papillary thyroid carcinomas (90%) had a score of 3 of 4; 43 of 53 benign lesions (81%) had a score of 1 or 2; and the thyroid lymphoma had a score of 2. The AUC for diagnosing malignant thyroid Xing et al—Strain Ratio in Differentiation of Thyroid Lesions

### Table 3. Sensitivity, Specificity, and Predictive Values Obtained Using the Strain Ratio Measurement Method and 4-Point Scoring System for Differentiation of Benign From Malignant Thyroid Lesions

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Method</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strain ratio</td>
<td>97.8</td>
<td>85.7</td>
<td>88.0</td>
<td>97.8</td>
</tr>
<tr>
<td>≤1 cm</td>
<td>4-point scoring system</td>
<td>88.8</td>
<td>81.1</td>
<td>80.0</td>
<td>89.5</td>
</tr>
<tr>
<td>&gt;1 cm</td>
<td>Strain ratio</td>
<td>92.3</td>
<td>86.4</td>
<td>89.6</td>
<td>91.7</td>
</tr>
<tr>
<td></td>
<td>4-point scoring system</td>
<td>91.3</td>
<td>71.4</td>
<td>77.7</td>
<td>88.2</td>
</tr>
<tr>
<td></td>
<td>Strain ratio</td>
<td>98.4</td>
<td>93.6</td>
<td>90.5</td>
<td>98.9</td>
</tr>
<tr>
<td></td>
<td>4-point scoring system</td>
<td>82.6</td>
<td>875</td>
<td>82.6</td>
<td>875</td>
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</table>

NPV indicates negative predictive value, and PPV, positive predictive value.

### Discussion

Sonoelastography is a new procedure that measures tissue elasticity by distorting the tissue structures using external pressure. Because softer parts of tissue deform more readily than stiffer parts, this technique enables objective evaluation of tissue stiffness from deformation rates. Currently, this tissue distortion can be displayed directly in terms of a color-coded overlay on a B-mode image (Figure 1). To date, the most important applications of elastography included examining breast nodes.\(^{14,15}\) Sonoelastography of the thyroid is a new procedure. In all previous investigations, the elastograms were divided by the respective examiners into 4 to 6 groups according to their specific color patterns.\(^{9–12}\) On the basis of our preliminary experience, we chose the 4 color patterns proposed by Rubaltelli et al\(^9\) as a reference.

In our study, 40 of 44 papillary thyroid carcinomas (90%) had a score of 3 of 4; 43 of 53 benign lesions (81%) had a score of 1 or 2; and the thyroid lymphoma had a score of 2. The AUC for diagnosing malignant thyroid
nODULES. These results agree with those of Rubaltelli et al.⁹ We also found that the strain ratios were different in benign and malignant lesions. While evaluating this method, we found that 3.79 was the best cutoff point for all of the lesions, with sensitivity of 97.8% and specificity of 80.7%. Using the strain ratio assessment method, the strain ratio had better diagnostic performance than the 4-point scoring method. According to ROC analysis, the best cutoff values for large and small nodules were different. Whether different-size nodules should or not use the same cutoff value needs further study in larger samples.

In this study, there was an overlap of elasticity between benign and malignant thyroid lesions; the strain ratios of 5 benign lesions were found to be greater than 3.79. Two of the 5 benign lesions contained clustered areas of microcalcification, which might have altered the stiffness of the nodules. Apart from this, an atypical adenoma and 2 subacute thyroiditis nodules had increased stiffness. Some reports indicate that subacute thyroiditis nodules have greater hardness because of histologic changes (disappearance of the follicular epithelium, replaced by a rim of histiocytes and giant cells, interstitial fibrosis, infiltration of lymphocytes, and plasma cells).

Vorländer et al.¹⁶ used the strain value of the region of interest from a lesion (as for region A in our study) instead of the strain ratio to differentiate malignant from benign lesions. They divided the lesions into 3 groups: hard (strain value, <0.15), intermediate (strain value, 0.16–0.3), and soft (strain value, >0.31). All of the lesions in the soft group had benign histologic results (NPV, 100%); and 70% of the carcinomas had a value of 0.15; and the diagnostic performance was good. Lyshchik et al.¹⁷ calculated the thyroid-to-tumor strain ratio and chose 4 as the best cutoff value.

**Figure 3.** Papillary thyroid carcinoma in a 38-year-old woman. The lesion had a score of 4 (malignant) on the 4-point scoring system. The strain ratio was 4.36 (malignant).

**Figure 4.** Receiver-operating characteristic curves for sonoelastography in differentiating malignant from benign lesions. A. Lesions smaller than 1 cm (area under the curve, 0.89). B. Lesions 1 cm or larger (area under the curve, 0.94).

<table>
<thead>
<tr>
<th>Size</th>
<th>Cutoff Value</th>
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<tbody>
<tr>
<td>All</td>
<td>3.79</td>
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<tr>
<td>≤1 cm</td>
<td>4.21</td>
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<tr>
<td>&gt;1 cm</td>
<td>3.98</td>
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**Table 4.** Optimal Cutoff Values for Different Thyroid Nodule Sizes According to Receiver Operating Characteristic Curve Analysis
This criterion had 96% specificity and 82% sensitivity. In our study, 3.79 was the optimal cutoff point, with specificity of 97.8% and specificity of 80.7%. These studies show the excellent diagnostic performance of strain ratios; however, the optimal strain ratio cutoff value needs to be confirmed in further studies. Kagoya et al measured the strain ratio using the sternocleidomastoid muscle as a reference irrespective of nodule size. A strain ratio of greater than 1.5 was set as the predictor of thyroid malignancy, but the diagnostic performance was not optimal. Considering the sternocleidomastoid muscle as a reference, the size and location of the nodules must be fully considered to avoid having a region of interest that is too large. Therefore, we need to further ascertain whether the sternocleidomastoid muscle is a suitable reference.

In this study, we measured the strain rates of thyroid nodules. During the procedure, the following points should be noted: First, horizontal and sagittal slices were both suitable, and we chose the most satisfactory image. Cross-scanning, however, is more susceptible to the impact of the carotid artery pulse, so most of the cases were examined by longitudinal scanning. Second, the region of interest should be controlled such that it is not too large and includes only the nodule and ample surrounding thyroid tissue because the carotid artery and unnecessary parenchymal tissue influence the strain distribution. Sonoelastography also has certain restrictions. Nodules in the thyroid isthmus or lower pole may not produce satisfactory images because of the tracheal clavical cartilage, and sonoelastography cannot be used to evaluate nodules with macrocalcification and predominantly cystic lesions. Although sonoelastography shows remarkable prospects, in some cases it still has limited applications.

This study had some limitations, which need to be addressed. First, only 1 lymphoma was included in this study group. We are still uncertain whether elastography has limited capabilities in differentiating follicular and medullary carcinomas. Second, our study included a relatively small number of cases, and strain ratios need to be confirmed in further studies with larger samples. Third, complex and partially cystic lesions were not included in this study, and the application of elastography in those types of lesions requires future studies. We also did not measure interobserver and intraobserver reliability. For thyroid cancer diagnosis, further studies evaluating interobserver and intraobserver variability and the reliability of sonoelastography are necessary.

In conclusion, the strain ratio assessment method can semiquantitatively evaluate the stiffness of solid thyroid lesions using the surrounding thyroid tissue as a reference. It is simple and convenient for clinical use. With 3.79 as the cutoff point, we could accurately identify malignant and benign lesions. Therefore, the sonoelastographic strain index can be used as a supplementary measure for differentiating benign and malignant thyroid lesions.

References


