The value of strain ratio in differential diagnosis of thyroid solid nodules

Chun-Ping Ning, Shuang-Quan Jiang, Tao Zhang, Li-tao Sun, Yu-Jie Liu, Jia-Wei Tian

Department of Ultrasound, Second Affiliated Hospital of Harbin Medical University, Harbin 150081, PR China
Department of Biostatistics, Harbin Medical University, Harbin 150081, PR China

Abstract

Objective: To assess the clinical value of strain ratio in differentiating thyroid solid nodules and explore its distribution characters based on pathological results.

Materials and methods: The study was approved by the ethic committee and the informed consents were signed. Ninety nine solid thyroid nodules (67 benign and 32 malignant) from 71 female (mean age 46.3 ± 9.8 years) and 28 male (mean age 54.9 ± 11.7 years) patients were evaluated. Five radiologists evaluated the nodules based on a four-degree elastography score system. Strain ratio was calculated on-line. Diagnostic performances of the two evaluations were compared using Receiver Operating Characteristic (ROC) curves. Values of different pathological nodules were compared by one-way ANOVA.

Results: Areas under the ROC curve (AUC) of the five readers were 0.82, 0.81, 0.79, 0.73 and 0.83, respectively. The AUC of strain ratio evaluation was higher (0.88 vs. 0.79, p < 0.001) than that of the ES score evaluation. Best cut-off points of the two evaluations were 3.5 (82% sensitivity, 72% specificity) and 4.225 (81% sensitivity, 83% specificity), respectively. Both the ES score and strain ratio were higher for malignant nodules than that for benign ones (p < 0.001).

Conclusions: Strain ratio was a useful index in differential diagnosis of thyroid solid nodules. It can provide quantitative information on thyroid nodule characterization and improve diagnostic confidence. The best cut-off point for benign and malignant nodules was 4.2.

Keywords: Ultrasound Elastography Strain ratio Thyroid

1. Introduction


Strain ratio is a new index that has been recently developed. It allows a quantitative analysis of the tissue stiffness. To be precise, strain ratio is a ratio obtained by dividing the mean strain within the lesion by the mean strain of the surrounding normal tissue. Few data has published about this index. An article published in 2008 had used this index to evaluate breast solid lesions [5]. Another article presented two cases reflecting the usefulness of this technique in differential diagnosis of solid pancreatic masses [6]. However, no effort has been made on the feasibility of applying the index to evaluating thyroid nodules.

This study is to explore the value of strain ratio in depicting the benign and malignant thyroid solid nodules. It is also intended to gain knowledge of ES characteristics of different pathological nodules. Many reports have demonstrated that solid nodules are more likely to be malignant, therefore, we mainly focused on the solid nodules in this study.

2. Materials and methods

2.1. Patients

This study was approved by the ethic committee of the Harbin Medical University (HMU). The inclusion criterion was the presence of single solid lesions in one thyroid lobe. The exclusion criteria included: (1) lesions containing cystic part more than 10% of the volume; (2) nodules having egg shell calcifications; (3) masses occupying more than 80% volume of the thyroid lobe; and (4) nodules located in the isthmus or the pole of thyroid. Totally, one hundred and ninety six patients referred for ultrasound exami-
nations were recruited for this study during January–November, 2009. All of the participants signed the informed consents required by the human study committee before enrollment. All of them have normal thyroid function.

Seventy six of them were lost during following up (26 patients chose yearly ultrasound observation instead of invasive treatments, 7 patients gave up because of metastasis, 2 patients died, 41 did surgery in other hospitals whose pathological results were suspicious), 8 patients were excluded because of previous surgical history in the neck, 13 were excluded due to the failure of elastography examination (9 were too fat, 1 had neck deformity and 3 had nodules too deep). Finally, 99 patients (71 women, mean age 46.3 ± 9.79 years; range 11–67 years; 28 men, mean age 54.9 ± 11.7 years, range 29–81 years) with definite pathological results were evaluated in the study. The mean size of the nodules was 1.74 cm (range 0.77–2.64 cm).

2.2. Ultrasound examination

Both the conventional Ultrasonography (US) and the real-time ES were performed by the HITACHI Vision 900 system (Hitachi Medical System, Tokyo, Japan) equipped with a linear probe of 6–13 MHz. All the examinations were conducted and recorded by two skilled sonographers who were blind to the history and pathologic results. Both of them have more than 6 years’ experience in scanning and about 1 month’s special training in acquiring elastograms.

2.3. Imaging acquisition

The patients were asked to lie in the supine position with the neck slightly extended. A lot of ultrasound gel was put on the patients’ neck as a stand-off pad.

Based on our preliminary experiments, the probe should contact the skin lightly, as strong initial compression may increase the false-negatives. A region of interest (ROI) was set centered on the lesion including sufficient surrounding tissue and the great cervical vessels were avoided as much as possible.

The technique based on the detection of small deformations of the tissue caused by free-hand alternating pressure. The pressure was standardized by real-time measurement on a numerical scale which was displayed lateral to the elastograms. An appropriate pressure was defined as a pressure which can sustain the number of the scale between 2° and 4° for 3 s at least. Multiple frames were acquired and many elasticity images were generated by comparing two adjacent frames during compression–relaxation cycles. Elastograms and the two-dimensional (2D) sonograms formed from the same radiofrequency were displayed side by side on the screen to aid in lesion identification. The deformity was represented by a 256 levels color (red–green–blue) map which was transparently overlaid on the 2D sonogram. Average strain of the ROI was colored in green. Hard tissue areas were shown in dark blue and soft tissue areas in red (see Fig. 1).

Here, the best-fit 2D sonogram–elastogram image pairs should match all of the following: (1) capsule of the thyroid and the connective tissue surrounding the gland displays a red ribbon; (2) thyroid tissue surrounding the nodules shows homogeneously green; (3) cervical muscles beside the gland demonstrate homogeneously green too.

On average, 4 (range 2–6) clip images and 9 (range 6–11) static images were obtained per nodule for further evaluation. Totally, 945 static images and 564 dynamic views were obtained from the 99 nodules. All of them were stored in the formats of JPG and AVI based on the case as a unit.

2.4. Elastogram review

2.4.1. Evaluation based on ES scores

Five radiologists who did not perform the examinations were invited to analyze the cases independently without knowing pathological results. All of them had more than 6 years’ experience of thyroid ultrasound examinations. Each nodule was assigned an elasticity score based on a four-point scale similar to the classification proposed by Itoh et al. [3]. A score 1 indicates even strain for the entire lesion. A score 2 is assigned to nodules with presented elasticity in a large portion of the examined area. A score 3 is assigned to nodules with presented stiffness in a large portion of the examined area. A score 4 indicates no strain in the entire nodule (see Fig. 1).

2.4.2. Evaluation based on strain ratio

This evaluation was performed during the examination by the sonographers using software equipped with the machine. The best-fit 2D sonogram–elastogram image pairs were selected to assign the strain ratio evaluation. Firstly, the operators were asked to trace an area A manually along the borderline of the lesion. Then an area B was selected just beside the target lesion as a reference. As strain varies as a function of depth, we just chose the homogeneous thyroid tissue at the same depth with the lesions as the reference tissue. The software would calculate the strain ratio automatically. Each lesion was assessed at least three times based on different static images and the average value was recorded as the final result. It would take the radiologists about 3–5 min per patient to perform the examination and evaluation.

2.4.3. Pathological examinations

Seventy eight patients accepted the ultrasound-guided fine-needle aspirates (FNA) in seven days after the ultrasound examination. Twenty four patients whose cytologic results were malignant or indeterminate accepted the surgical treatment. The other 21 patients refused FNA and accepted the thyroidectomy directly. After being fixed and embedded, the specimens were cut into thin slices and stained with standard hematoxylineosin. During histological examination, three slices per nodule were examined by two independent pathologists who had 10 years experience according to the surgical pathology [7]. When there was discordant, a third pathologist was invited and the agreement was found by rereading the slices together. All the subjects with benign results were re-examined by Ultrasound after 6 months.

2.5. Statistical analysis

The diagnostic performances of the two evaluations were evaluated by Receiver Operating Characteristic (ROC) curves. Area under ROC curve (AUC) and the standard errors were derived using the bootstrap resampling approach with 5000 repeats. The Z-test was employed to compare the diagnostic performances of two evaluations based on the bootstrap samples. Meanwhile, to access the stiffness of different pathological nodules, we compared the distribution of the mean ES scores and strain ratio values using one-way ANOVA. The graphs were made by MATLAB Version 7.10.0.499(R2010a). Statistical analysis was performed using SAS version 9.1.3 (SAS Institute, Inc., Cary, NC, USA). A two-tailed p < 0.05 was considered to be statistically significant.

3. Results

3.1. Pathologic results

Totally, 67 benign nodules and 32 malignant nodules were evaluated. There were 54 nodular goiters, 13 adenomas in the benign
Fig. 1. Examples of elastograms accompanied with pathological images. The images were elastograms, B-mode sonograms and pathological images from left to right. There was a color bar and a press scale on the right side of every elastogram. The area A and area B outlined for the strain ratio evaluation were marked in yellow. The pathology images were hematoxylin–eosin stained, and the original magnification was 10× for cases A–C and 20× for case D. (A) A case of nodular goiter. All the five readers scored the nodule as 1. The average strain ratio was 1.31. (B) A thyroid adenoma from a 39-year-old woman. The five experts scored the nodule as 2. The average strain ratio was 1.67. (C) A nodular goiter with a mean elasticity score of 3 in a 57-year-old man. The average strain ratio was 1.43. (D) A papillary carcinoma with elasticity score of 4 in a 61-year-old woman. The average strain ratio of the nodule was 6.77.

group. Most of the malignant masses were papillary carcinomas (21/35), 4 microcarcinomas were found by the ultrasound-guided FNA and 3 microcarcinomas coexisted with nodular goiters were diagnosed by surgical treatment. Four cases of other malignant nodules were evaluated, including 2 metastatic carcinomas (one from the throat and the other from the lung), 1 follicular carcinoma and 1 medullary carcinoma.

3.2. ROC analysis

AUC were 0.82, 0.81, 0.79, 0.73 and 0.83, respectively for the five observers. Comparison between the two evaluations was shown in Fig. 2. It was obvious that AUC of the strain ratio evaluation was much higher than that of the ES score evaluation (0.7929 vs. 0.8803, Z = 211.26, p < 0.0001). The best cut-off points for differentiating benign and malignant nodules were 3.5 (sensitivity = 82.4%, specificity = 71.6%) for the ES scores evaluation and 4.225 (sensitivity = 81.8%, specificity = 82.9%) for the strain ratio evaluation (shown in Table 1).

3.3. Distribution of ES scores and strain ratio of the nodules

ES scores and strain ratio of different pathological nodules were different (shown in Figs. 3 and 4). Most of the benign nodules were scored 2 (including 26 cases of nodular goiter and 6 cases of adenomas,) and 3 (including 14 nodular goiters, 4 adenomas). Nine cases of thyroid goiters were scored 4 and 3 cases were scored 1. Most of the malignant nodules were scored 4, including 20 cases of papillary carcinomas, 6 cases of microcarcinomas and 3 cases of other malignant nodules. The mean score
Table 1

<table>
<thead>
<tr>
<th>Evaluations</th>
<th>Cut-off point</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>AUC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation based on the ES scores</td>
<td>3.500</td>
<td>82.4</td>
<td>71.6</td>
<td>0.7929</td>
<td>0.7325–0.8492</td>
</tr>
<tr>
<td>Evaluation based on the strain ratio</td>
<td>4.225</td>
<td>81.8</td>
<td>82.9</td>
<td>0.8803</td>
<td>0.8110–0.9390</td>
</tr>
</tbody>
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Fig. 2. Comparison of the Receiver Operating Characteristic (ROC) curves between the first and the second generation ES.

Fig. 3. Scatter plot graph demonstrates the distribution of the average score of different pathologic nodules evaluated based on the ES score system. (•) Distribution of the benign nodules; (○) distribution of the malignant nodules; (...) the best cut-off point (ES = 3.5).

4. Discussion

Thyroid cancer incidence rose more than 2-fold from 1973 to 2002, while the mortality rates remained relatively constant. When the data were analyzed by histological type and tumor size, the increase appeared predominantly among small (<2 cm) papillary carcinomas [1], likely owing to increased identification secondary to the availability of high resolution ultrasound. Ultrasonography was recommended as a noninvasive technique by the three recent guidelines on thyroid diagnose published in 2006 [8–10] and the revised guideline published in 2009 [11]. Moon’s study [12] concluded that calcifications, taller-than-wide shape and speculated margin were the specific criteria for malignant nodules, while spongiform appearance and isoechogenicity were indicators for benign nodules. However, no single US features suggestive of malignancy had an overall diagnostic accuracy higher than 75% and no conventional US features could display the elasticity information.

4.1. Elastography

Elastography can provide information about tumor hardness which was considered to be an indicator of malignancy. This technique is based on the Combined Autocorrelation Method (CAM) [13] which can detect the strain of the tissue in real time and the Expanded Combined Autocorrelation Method (ECA).

Until now, there were two kinds of evaluation about the elastography. One was based on the ES scores and the other was based on the strain ratio. This study evaluated the usefulness of strain ratio in the differential diagnosis of thyroid nodules, compared with for benign nodules and malignant ones was significantly different (2.67 ± 0.86 vs. 3.86 ± 0.43, p < 0.001). The same distribution characters were found in the strain ratio analysis. Differences between the benign and malignant nodules were significant too (2.59 ± 2.12 vs. 9.10 ± 7.02, p < 0.001). By pathological type, strain ratio was 2.05 ± 1.33 for nodular goiters, 2.37 ± 1.21 for thyroid adenomas, 5.04 ± 3.38 for micro papillary carcinomas, 8.5 ± 6.2 for papillary carcinomas and 21.4 ± 4.79 for other malignant carcinomas.
the evaluation according to ES score system. The ES score evaluation based on the color distribution which was superimposed on the B-mode image. It was prompted to be an efficient way by several reports [14,15]. However, only sketchy knowledge about the stiffness of the target mass can be provided.

On the contrary, strain ratio was a quantitative index which can provide accurate information. It was known since 1991. Ophir et al. reported [16] that successful quantitative strain measurement was possible, repeatable, and reliable if it had a uniform stress case. In 2007, Koji Waki and Takeshi Matsumura [17] did a research using a quantitative phantom and an automatic compressor. He demonstrated that regardless of stress, the strain ratio showed constant properties and the value was shown to become large in accordance with the ratio of their elasticity. Unlike breasts, thyroid is a superficial convex gland located between the cervical vessels and trachea. The anatomical features make it difficult to apply uniform pressure. Therefore, a coupler was fitted at the tip of the transducer and a transparent solid nodule. As the National Cancer Institute reported, the strain ratio was a quantitative index which can provide enough reference tissue at the same depth with the lesions.

The earliest prospective clinical study was published in Radiology in 2005, in which Lysichik et al. [18] put forward three criteria of elastography including the strain index, the margin regularity score and the area ratio, and the strain ratio was considered to be the strongest independent predictor of thyroid gland malignancy. However, only 33 patients were included in the study. Our study, with a larger number of patients and more sophisticated method, described elastography characters of different pathological nodules in detail, and confirmed that elastography was useful in differential diagnosis of malignant thyroid nodules, especially those small papillary carcinomas (<1 cm). Furthermore, we compared the clinical values of the two evaluation methods of elastography.

4.2. Clinical value of strain ratio

Compared with the ES score system, the AUC of the strain ratio evaluation was higher. When we choose 4.2 as the cut-off point for malignant and benign disease, the sensitivity and specificity was 82.4% and 71.6%, respectively. However, selection of the reference tissue may affect the results. Zhi et al. [5] recommended breast tissue at the same depth with the lesions to be the reference. Rago et al. [14] indicated that the predictability of elastography was independent of the nodular size and position. In this study, we also chose the thyroid tissue in the same depth with the target nodule as reference. Results showed that both the score and the strain ratio were repeatable and reliable. The longitudinal view of the thyroid was recommended for it can provide enough reference tissue at the same depth with the lesions.

Distribution of the strain ratio value confirmed that benign nodules are much softer than the malignant ones. Most of the papillary carcinomas demonstrated thorough and steady blue in elastograms, the value of strain ratio was quite high too. About the micro-papillary carcinomas, solitary ones are easily distinguished because they demonstrated lone blue nodules in a green background (thyroid). However, when coexisted with other pathological changes such as nodular goiters, differential diagnosis of microcarcinomas would be quite difficult and ultrasound-guided FNA would be necessary. In our study, there were 3 cases of micro papillary carcinomas which were scored as 3, and the strain ratio were 1.86, 1.74 and 2.9, respectively. All of them were misdiagnosed as benign before FNA. Pathological examinations showed that these microcarcinomas were surrounded by fibrotic thyroid tissue and nodular goiters.

Most of the nodular goiters were scored 2 (26/51) and 3 (14/51), the mean strain ratio was 2.05 ± 1.33. However, 3 cases were scored 1 and their strain ratios were 1.96, 2.87 and 0.65, respectively. Pathologists explained that this may be associated with the adenomatous changes in the nodular goiters. Meanwhile, fibrosis changes and calcifications can make the goiters stiffer. That is why nine cases of this study got a score of 4 in the evaluation. Most of the adenomas were scored 2 (5/12) and 3 (4/11). None of the adenomas were scored 4.

4.3. Limitations of the index

Strain ratio was obtained by dividing the mean strain within the lesion by the mean strain from the surrounding tissue. So, sufficient surrounding tissue was essential. To our experience, if the volume
of the nodule was too large, uniform pressure would be difficult to perform, and the value of strain ratio would be questionable. Selection of the reference tissue was important, and homogeneous thyroid tissue at the same depth with the target nodule was recommended. The calculation of strain ratio can only be performed during the examination, and off-line evaluation was denied. Fortunately, it is not time-consuming. As this evaluation based on static images instead of dynamic clips, selection biases would be inevitable. It is possible that computer-aided off-line elastography can solve this problem.

4.4. Limitations of the study

Two limitations in this study should be addressed. First of all, we just concentrated on solid nodules, regardless the cystic and mixed nodules. It was reported that most of the cystic and predominant cystic nodules are benign, and the cystic part demonstrated BGR (blue–green–red) phenomenon in elastograms. Next, this study simply did not include any data about the morphology of the lesions on conventional US. As the elastogram was in fact a color map transparently imposed on the conventional US, the diagnosis of the radiologists would be inevitably affected by the characteristics of the 2D sonograms. However, several researchers agreed that elastography can provide a useful adjunct in sonographic evaluation. Rago et al. [14] reported that the prediction of the highest elasticity scores was independent of nodular size with sensitivity of 100% and specificity of 100%.

In conclusion, the strain ratio is a useful index in the differential diagnosis of thyroid nodules, since it can provide quantitative information about the stiffness of the nodules. The best cut-off point for benign and malignant nodules is 4.2.

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