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ORIGINAL ARTICLE

Role of ultrasound elastography in assessment of indeterminate thyroid nodules

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KEYWORDS

Ultrasound;
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Abstract *Purpose:* To evaluate the role of ultrasound elastography as an additional technique in differentiating US indeterminate thyroid nodules in order to decrease the number of tissue biopsies.
Methods: We evaluated 30 patients with 36 indeterminate thyroid nodules based on US, criteria, by US elastography, using both the elastography score and strain ratio. Baseband US data were downloaded for off-line analysis. Elastographic maps (color coding) and thyroid stiffness index (strain ratio) were calculated for all nodules, with histopathological results being the standard reference. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff strain ratio for separating benign and malignant thyroid nodules.
Results: Malignant nodules had a higher degree of color and strain ratio compared to benign nodules, with a statistically significant difference ($p < 0.05$). Nodules with an elastography score of 2 were benign, while those with an elastography score of 4 and 5 were mostly malignant. Malignancy could not be excluded using ultrasound elastography criteria only, in nodules with a score of 3. The sensitivity and specificity of the US-elastography strain color coding for thyroid cancer diagnosis were 91% and 72% respectively. Using ROC analysis, the optimal cutoff strain ratio for separating benign and malignant thyroid nodules was found to be 1.6 with a calculated 89% sensitivity and 70% specificity. The overall accuracy of strain color was slightly better than strain ratio, 91% compared to 86% respectively.
Conclusion: Ultrasound elastography is an easy, non-invasive and rapid technique that can be routinely used in thyroid US scans to select cases for FNAC, and decrease the number of unnecessary biopsies, and consequently decrease the hazards and costs. However, future advances in image acquisition and reconstruction algorithms are required to improve the image quality and clinical usefulness of this technique.

1. Introduction

Thyroid nodules are very common and may be observed at ultrasonography (US) in 50% of the adult population (1).

Even though most of those nodules are benign, the possibility of cancer must always be considered (2). The imaging

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modality of choice for the investigation of thyroid nodules is high-resolution US, which has markedly improved the detection of thyroid nodules (3). Ultrasound can help in differentiating benign from malignant thyroid nodules. However, individual US features may be of limited value (4). Alternative ultrasound techniques are now being used to improve the diagnostic accuracy of ultrasound, as many suspicious ultrasound features can exist in both benign and malignant nodules (5).

Elastography is a newly developed dynamic technique that uses ultrasound to provide an estimate of tissue stiffness by measuring the degree of distortion under the application of an external force. Like palpation in the assessment of the thyroid during physical examination, elastography uses tissue deformation, or strain, caused by compression and is estimated by precompression and postcompression ultrasonic signals (6).

Using thyroid elastography, significant differences in stiffness between normal thyroid tissue and pathologic thyroid tissue have been found. Although US elastography is not yet used in routine clinical practice, it has been shown to be useful in the differential diagnosis of benign and malignant lesions of the breast (7) and prostate (8).

US elastography is nonstressful for patients, is easy to perform, and requires no more than a few minutes of additional examination time compared with that of conventional US (2). The purpose of our study was to evaluate the role of US elastography as an additional technique in differentiating US indeterminate thyroid nodules in order to decrease the number of tissue biopsies.

2. Patients and methods

2.1. Patients

The study included 30 consecutive patients, including 25 women and 5 men (age range, 23–67 years). They were referred to the Ultrasound Unit at a special radiology center between September 2013 and February 2015. Patients with purely cystic nodules, anechoic nodules without solid components, or with eggshell-calcified nodules were excluded from the study. Each patient signed an informed consent before being enrolled in the study. Most of the patients had multiple thyroid nodules; however, we selected the most indeterminate pattern for the nodule to be enrolled in our study, based on the Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules (9), which included the following US features as suspicious or indeterminate: microcalcifications; hypoechogenicity, increased nodular vascularity; infiltrative margins and taller than wide on transverse view (Table 1). The presence of at least one of these indeterminate/suspicious features was sufficient for selection of the nodule in the study. We also included nodules with an absent halo sign, which is considered as an additional, but valuable criterion as well (10). 36 Nodules in these patients were examined by US-elastography. All nodules were subjected to fine-needle aspiration cytology, taken from each nodule separately and patients with a reading of malignant or indeterminate had thyroid surgery.

2.2. Real time ultrasound and US elastography

B-mode ultrasound was performed first for all nodules, followed by color-power Doppler. The following US parameters were evaluated in all thyroid nodules: presence or absence of the halo sign, the margins (regular or irregular), the relation between the height and width of the nodule and the presence or absence of microcalcifications. Micropure imaging was applied to help detect microcalcifications. Micropure imaging algorithm (Toshiba) (11) is an adapted filter that is used to enhance bright echoes to visualize and show calcifications, particularly microcalcifications. Positive blood flow, whether perinodular or intranodular, on color Doppler was also documented. Only nodules with an indeterminate or suspicious feature were further evaluated by ultrasound elastography, and an elasticity score and strain ratio index were determined for each nodule. All patients were examined with a 10–13-MHz. linear transducer (Hitachi medical system EUB 7000/Toshiba Aplioi XG machine). The transducer was applied to the neck using adequate amount of gel, the neck was hyper-extended and the chin was elevated. The grayscale sonography and elastography were performed by the same radiologist in all patients, to prevent differences among operators and to standardize the degree of manual pressure. The pressure, which was able to sustain the scale number between 2 and 4, for a minimum of 3 s, was set as the optimal pressure. The region of interest (ROI) was centered on the lesion, including sufficient surrounding thyroid tissue. Patients were asked to try to avoid swallowing during the examination to minimize movement of the thyroid gland.

Table 1 The Correlation between Conventional ultrasound and Doppler findings of thyroid nodules, with the pathological diagnosis.

Features *n*(%)	Cytology		
	Benign	Malignant	
Halo sign			
Absent	3(13%)	12(92%)	0.000 (HS)[a]
Present	20(86.9%)	1(8%)	
Margin			
Irregular	19(82.6%)	9(69.3%)	0.39 (NS)[a]
Regular	4(17.4%)	4(30.7%)	
Height and width			
Wider than tall	21(91.3%)	7(53.8%)	0.44 (NS)
Tall than wide	2(8.7%)	6(46.2%)	
Calcification			
Absent	18(78.2%)	7(53.8%)	0.11 (NS)
Present	5(21.7%)	6(46.2%)	
Doppler			
No flow	4(17.5%)	0	0.22 (NS)
Perinodular	11(47.8%)	5(38.4%)	
Intranodular	8(34.7%)	8(61.5%)	

[a] HS = highly significant value, NS = non-significant value.

2.3. Elasticity scores in thyroid nodules

Ultrasound elastography was color coded between red (softest component) and blue (hardest component) based on five point scale according to the classification proposed by Yerli et al. (12):

Score 1: Diffuse elastic pattern (homogeneously diffuse green).

Score 2: An almost entirely elastic pattern (almost entirely green with some blue points).
Score 3: Mosaic of green and blue, but mostly elastic pattern (mostly green).
Score 4: Mosaic of green and blue, but most of the lesion had no strain (mostly blue).
Score 5: No strain (diffuse or almost entirely blue, and there might also be a blue rim surrounding the lesion).

2.4. Strain ratio of thyroid nodules

By dividing the strain value of normal tissue by the stain value of the nodule, the strain ratio is determined. The borders of the lesion are manually traced, and the adjacent thyroid tissue is used as a reference, to estimate the strain ratio automatically, using a special software, within the ultrasound machine.

2.5. Histopathological diagnosis

All of the patients underwent fine-needle aspiration of the suspicious thyroid nodules, under ultrasound guidance within days of the real-time sonographic elastographic evaluation. Patients with a reading of malignant or indeterminate had thyroid surgery. The pathological diagnoses of the thyroid nodules were compared with the B-mode sonographic features, the elastography scores and strain ratio of the nodules.

2.6. Statistical analysis

Multivariate logistic regression analysis was performed to assess the independent variables for malignancy prediction. Analysis of data was done using SPSS (statistical program for social science version 16) as follows: description of quantitative variables as mean, SD and range, as well as description of qualitative variables as number and percentage. Unpaired *t*-test was used to compare two groups as regards quantitative variable. Diagnostic performance was evaluated with receiver operating characteristic (ROC) curve analysis, used to find out best cutoff value and validity parameters.

3. Results

3.1. Demographic characteristics

30 patients, with 36 indeterminate thyroid nodules, 25 women (83%) and 5 men (17%), age range, 23–67 years, with a mean age of 42 years were enrolled in this study. 3 patients had more than one indeterminate nodule; in 2 patients, the nodules were bilateral.

3.2. Pathological diagnosis

Out of a total of 36 nodules, 13 nodules (36.1%) had a final pathological diagnosis of malignancy, 12 papillary thyroid carcinomas (including 10 classic variant and 2 follicular variant) and 1 undifferentiated carcinoma. 23 nodules (63.9%) were benign at histology: 9 multinodular goiter, 7 adenomas, 4 hyperplastic nodules, 2 colloid cysts and one lymphocytic infiltration.

Table 2 Elastography scores of benign and malignant thyroid nodules.

Elastography score	Total number, *n*(%)	Benign, *n*(%)	Malignant, *n*(%)
1	–(0%)	–	–
2	16(44%)	16(100%)	–
3	11(30.6%)	6(54.5%)	5(45.6%)
4	8(22.2%)	1(12.5%)	7(87.5%)
5	1(3.8%)	–	1(100%)

Table 3 Strain ratio of benign and malignant thyroid nodules.

Strain ratio	Total number, *n*(%)	Benign, *n*(%)	Malignant, *n*(%)
⩽1.6	19(52.7%)	18(94.7%)	1(5.3%)
> 1.6	17(47.2%)	5(29.4%)	12(70.6%)

3.3. Conventional ultrasound and doppler findings

This table shows that nodules with an absent halo sign had a higher frequency of malignancy, than those with a halo sign, with a significant difference (by using Fisher's exact test). There was no significant difference with the other findings.

3.4. Elastography scores of thyroid nodules

Of the 36 nodules, none of the nodules had a score of 1, 16 nodules (44.4%) had a score of 2, 11 nodules (30.6%) had a score of 3, 8 nodules had a score of 4 (22.2%) and one nodule had a score of 5 (3.8%) (see Tables 2 and 3).

All 16 Nodules having a score of 2, were benign (Fig. 1). Out of the 11 Nodules having a score of 3, 6 nodules were benign (Fig. 2), while 5 nodules were malignant (Fig. 3), 7 nodules out of 8 scoring 4 were malignant (Fig. 4), while only one was benign. The single nodule having a score of 5 was malignant (Table 2). Score 2 was only seen in benign nodules, Score 3 was seen in both benign and malignant nodules, while scores 4 and 5 were significantly seen in malignant nodules ($p < 0.05$) with a sensitivity of 91% and a specificity of 72%. The positive and negative predictive values were 83% and 92% respectively. The accuracy of the technique was 91% (Table 4).

3.5. Strain ratio of thyroid nodules

Benign nodules had a mean strain ratio of 1.72 ± 0.35, while malignant nodules had a mean strain ratio of 3.12 ± 0.84, thus showing a significant difference ($p < 0.001$).

The mean SR was 1.23 ± 0.62 for nodular goiters, 1.12 ± 0.78 for hyperplastic nodules, 1.41 ± 0.56 for thyroid adenomas, 2.74 ± 1.12 for papillary carcinomas, and 2.95 ± 1.31 for undifferentiated carcinomas. Receiver operating characteristic (ROC) analyses determined the optimal cutoff strain ratio to be 1.6 for the separation of benign and malignant thyroid nodules, with area under the curve (AUC) of 0.86 (0.79–0.93) for strain ratio (Fig. 5).

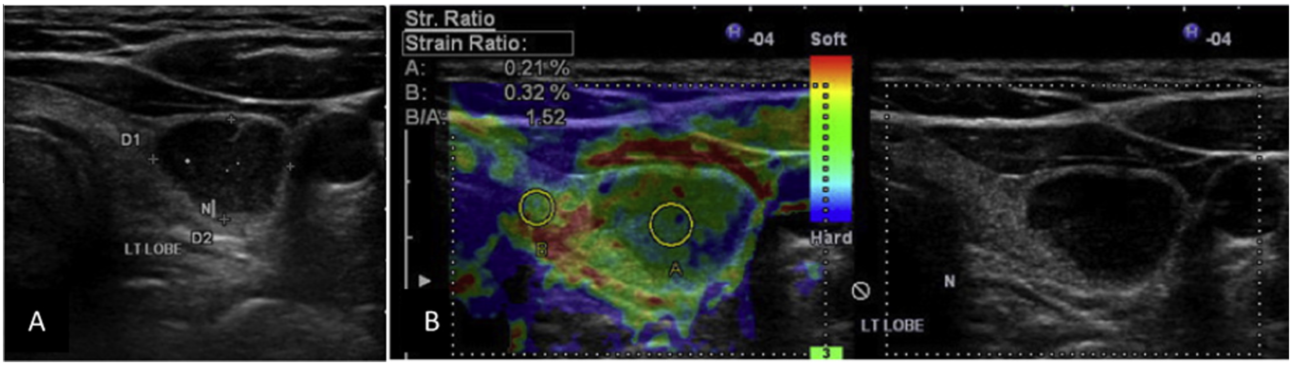

Fig. 1 B mode US image (A) showing a markedly hypoechoic nodule in the left lobe. Split screen US Elastogram and B-mode image (B), showing the hypoechoic nodule to be almost completely green with a few blue spots (score 2). The average strain ratio = 1.52. Histopathology revealed nodular goiter.

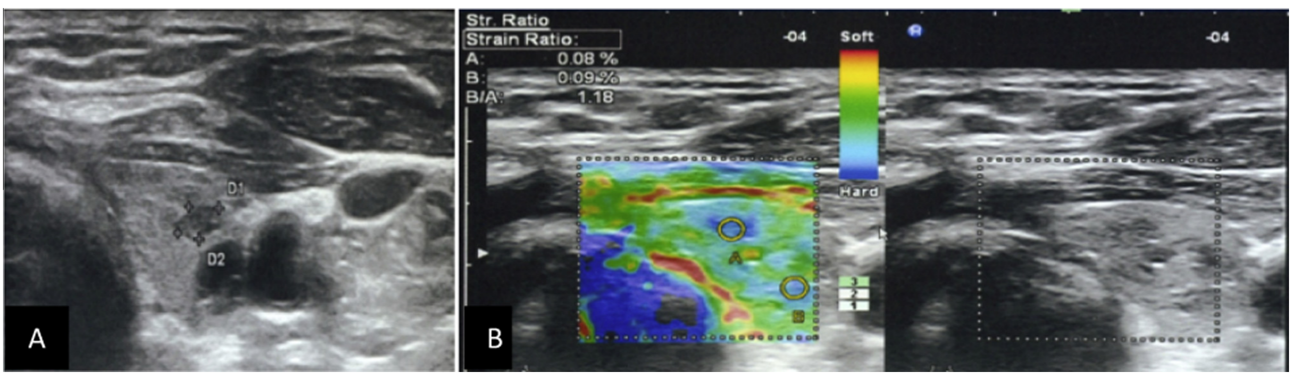

Fig. 2 B mode US image (A) showing a small irregular hypoechoic nodule in the left thyroid lobe. Split screen US Elastogram and B-mode image (B), showing the hypoechoic nodule to be mosaic green and blue (score 3). The average strain ratio = 1.18. Histopathology revealed follicular adenoma.

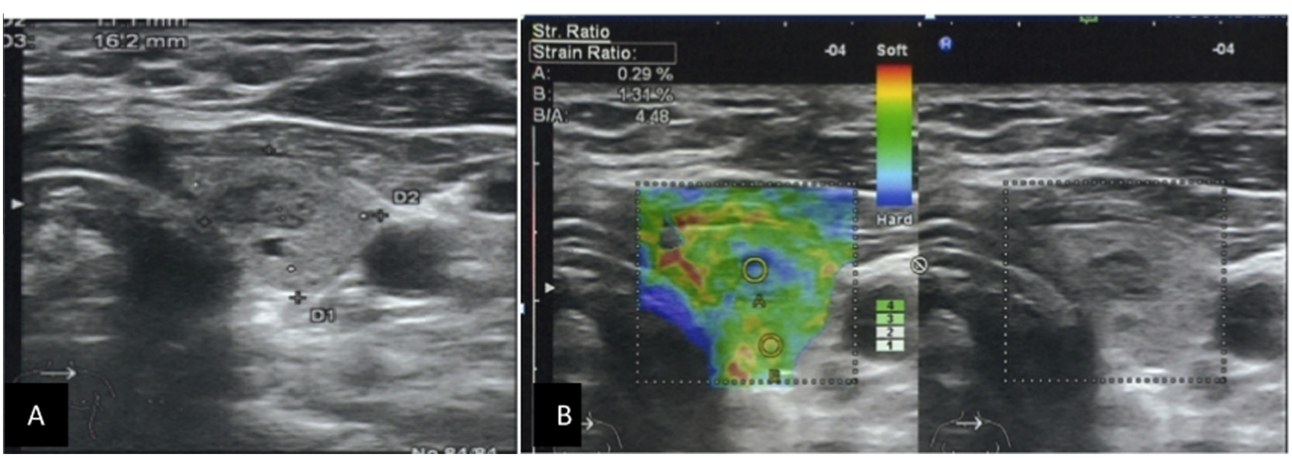

Fig. 3 B mode US image (A) showing a heterogeneous irregular hypoechoic nodule in the left thyroid lobe. Split screen US Elastogram and B-mode image (B), showing the hypoechoic nodule to be mosaic blue and green (score 3). The average strain ratio = 4.48. Histopathology revealed follicular variant of papillary carcinoma.

Regarding the quantitative evaluation by strain ratio, when using the cutoff value of 1.6, the sensitivity and specificity of the test were 89% and 70% respectively. The positive and negative predictive values were 78% and 90% respectively. The accuracy of the test was 86% (Table 4).

When comparing the diagnostic indices of strain color versus strain ratio (Table 4), we found that the elasticity score overall accuracy was slightly better than the strain ratio index, and that both of them were better positives (higher sensitivity) than negatives.

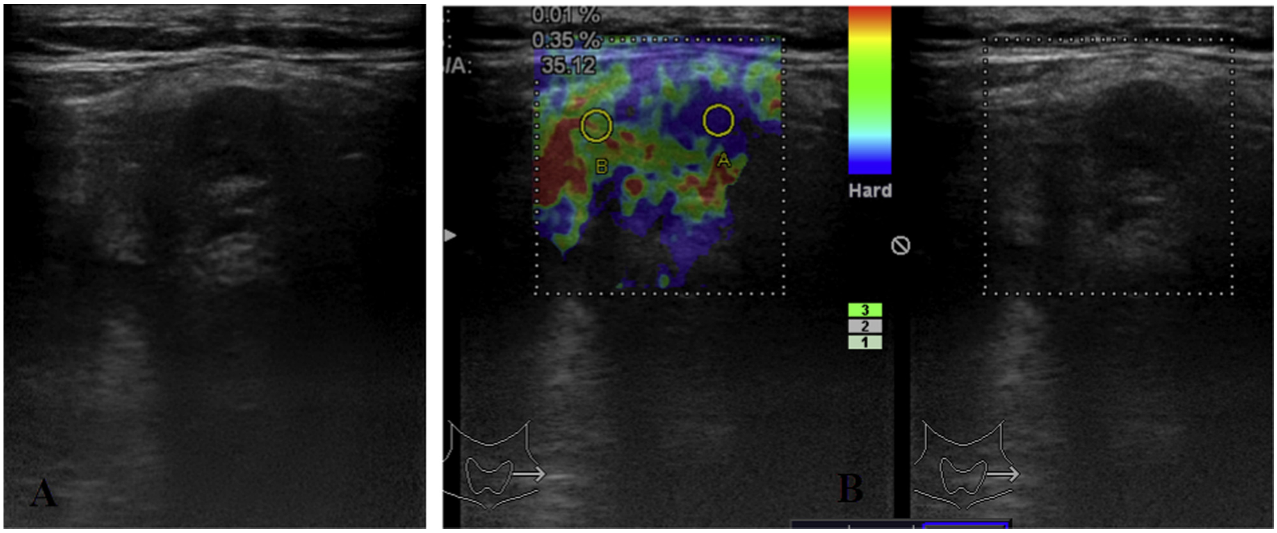

Fig. 4 B mode US image (A) and split screen US Elastogram (B) showing a hypoechoic nodule in the right thyroid lobe that displays mosaic green and blue (score 4). The average strain ratio = 3.8. Histopathology revealed papillary carcinoma.

Table 4 Comparison of the diagnostic indices of strain color and strain ratio index.

Diagnostic index	Elasticity score (%)	Strain ratio (%)
Sensitivity	91	89
Specificity	72	70
PPV (positive predictive value)	83	78
NPV (negative predictive value)	92	90
Accuracy	91	86

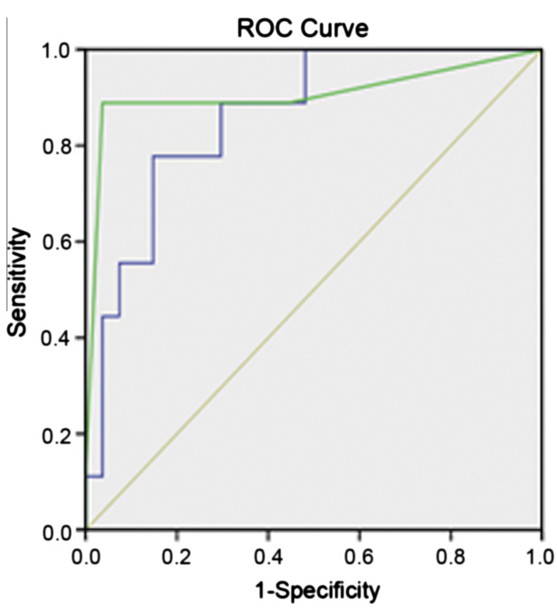

Fig. 5 Receiver operating characteristic (ROC) curve for determining the best cutoff strain ratio which differentiates between benign and malignant thyroid nodules. The area under the curve (AUC) was 0.86 (0.79–0.93).

4. Discussion

Nodular thyroid disease is a common finding, with thyroid nodules being palpable in 5% of subjects, but detectable by thyroid ultrasound (US) in up to 50% of the general population. However, only a minority of thyroid nodules are likely to cause significant health problems (13).

The Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer has indicated that FNAC is the most accurate and cost-effective method for evaluating thyroid nodules (9). However, the major limitation of FNAC cytology is that 10–15% of specimens are nondiagnostic, and 10–20% are indeterminate (13,14).

B mode ultrasonography is usually the first imaging method for evaluating thyroid nodules. There is a general agreement that ultrasound features indicating a high risk for malignancy should be an indication for FNAC and even further treatment such as surgery (6). Ultrasound features predictive of malignant nodules include the presence of irregular margins, marked hypo echogenicity, microcalcifications, taller-than-wide shape, absent halo sign and intranodular vascularity (9). In our study, absence of halo sign was the strongest independent factor indicating malignancy with highly significant difference (p value = 0.000), followed by presence of microcalcifications and margin irregularity of the thyroid nodule. Other US criteria were not associated with a significant dependent difference.

Kurita (14) evaluated the usefulness of MicroPure imaging in detecting the microcalcifications in breast lesions. They reported that MicroPure imaging improved the visualization of microcalcifications and suggested that this imaging algorithm is a clinically useful, easy, imaging technique in the diagnosis of microcalcifications. In our study, 8 of 36 nodules; 4 benign (17.3%) and 4 (30.7%) malignant thyroid nodules revealed calcifications. All microcalcifications were detectable using both B-mode and MicroPure imaging. However, they were much easily depicted with Micropure imaging (Fig. 5).

A major disadvantage of B-mode US, though, is its low specificity. Consequently, benign cytology is detected in most cases that have undergone FNAC on the basis of the findings of B mode US only (12), and the overall incidence of cancer in patients with thyroid nodules selected for FNAC is approximately 9.2%–13.0% (15).

In an attempt to increase the specificity of conventional US, US elastography was developed to determine tissue stiffness and strain information noninvasively. Strain represents the amount of deformation; thus, stiff tissue shows less strain than softer tissue. A thyroid lesion may have different levels of stiffness within it, depending on the cellularity and the composition of the nodule. Information from these elastograms helps to assess the relative stiffness of the lesion compared with its surrounding tissues and within itself (6).

There are two kinds of elastography (strain and shear wave elastography) that are currently used in clinical practice. In our study, we only used strain elastography as shear wave elastography software was not available in our equipment.

In strain elastography, two kinds of elasticity assessments can be obtained in sonographic devices equipped with specific software: first, visual scoring of colors within and around the nodules and second, a strain ratio, which is automatically calculated through the machine by drawing two regions of interest (ROIs) over the target region and the adjacent reference region, respectively. Similar to Lyshchik et al. (16) and Yerli (12), we used both methods of thyroid strain imaging in our study, real time elastography followed by off-line processing of strain images reconstructed from radiofrequency data stored during US examination, rather than real time processing.

Real-time strain imaging has some advantages over off-line elastography: It is easy to perform and requires no more than 3–5 min of additional examination time, it is noninvasive, and it is suitable for use during routine ultrasound examinations. In addition, this imaging technique facilitates the dynamic visualization of lesions during compression (17).

Off-line processing of strain images, however, involves the use of more sophisticated image-processing algorithms that increase image quality and spatial resolution. In addition, only with off-line processing, in this study, was it possible to quantitatively measure the stiffness of tissue, compare the stiffness of benign and malignant nodules with the stiffness of the surrounding normal parenchyma, and use the results of these measurements for the differential diagnosis. However, some authors considered this method more labor intensive and time consuming (16).

Dighe et al. (8) used the internal natural systolic pulsation of the carotid artery in the sonoelastographic examinations and determined a thyroid strain index that was computed as the ratio of strain near the main carotid artery to that of a low stiff region inside a thyroid nodule for the differential diagnosis of thyroid nodules. Lyshchik et al. (16) and Yerli et al. (12), used the external manual compression method regardless of the systolic or diastolic period in the elasticity evaluation of thyroid nodules and scored nodules according to visualization, relative brightness, and margin regularity and this is the method of compression we used in the current study.

Our study included 30 patients with 36 indeterminate thyroid nodules. Multivariate logistic regression analysis was performed to select elastographic criteria that were independently associated with thyroid cancer. We found that elasticity scores were significantly higher in malignant nodules than in benign nodules and normal thyroid gland (p value = 0.000) with a sensitivity and specificity of 91% and 72% respectively, and positive and negative predictive values of 83% and 92% respectively. These results are in agreement with Asteria et al. (18), who reported the sensitivity, specificity, PPV and NPV of ultrasound elastography for thyroid cancer to be 94.1%, 81%, 55.2% and 98.2% respectively, and also with Rago et al. (19), who showed a sensitivity and specificity as high as 97% and 100% respectively, using US elastography. Yet, they disagree with Jun-Mei Xu et al. (10), Moon et al. (20), and Vorlander et al. (21), who concluded that US elastography imaging was not significantly associated with thyroid malignancy.

A wide range of strain index values have been suggested as a cutoff value in differentiating benign from malignant thyroid nodules. Lyshchik et al. (16), suggested that a strain index value greater than 4 is the strongest independent predictor of thyroid gland malignancy ($p < 0.001$) and exhibits 96% specificity and 82% sensitivity. Kagoya et al. (2), concluded that a strain ratio or strain index value greater than 1.5 is a predictor of thyroid malignancy and exhibits 90% sensitivity and 50% specificity, which is in concordance with our results, that showed a strain index higher than 1.6, to be an independent predictor of thyroid malignancy, with sensitivity and specificity of 89% and 70% respectively.

Our results actually do not match those of earlier studies (22,23) which concluded that the diagnostic performance of strain ratio in differentiating benign from malignant nodules was higher than elastography scoring, as we found out that elastography scoring overall accuracy was slightly better than strain ratio, 91% compared to 86% respectively.

Several factors can affect the results of elastography, including nodule characteristics (calcifications and cystic components), the experience of the operator, and motion artifacts such as carotid artery pulsation (24).

To overcome these limitations, elastography can be selectively used in thyroid nodules without calcifications and cystic changes, and should be performed by experienced operators using objective parameters provided by elastographic machines (25). In our study we included predominantly solid thyroid nodules with indeterminate criteria for malignancy, by US basis, and initially excluded all the purely/predominantly cystic nodules as well as nodules with eggshell calcifications.

In spite of the fact that the group of patients with multinodular thyroid, may represent up to 40% of all patients referred for thyroid nodules, we totally agree with Bercoff et al. (26) who suggested that many cases of multinodular goiter are not suitable for elastography because the nodule to be examined with this technique must be clearly distinguishable from other nodules in the thyroid gland. They also added that with nodules having a diameter greater than 3 cm, adequate compression of the whole nodule may not be obtained. However we did not find it to be a major limitation in our study.

One of the limitations of our study was that the study group included selected patients with indeterminate thyroid nodules, which could represent a bias that amplifies the predictive value of US elastography. Another limitation was that the sonoelastographic and B-mode sonography images were in the same scan plane due to use of split screen method in most of the machines during sonoelastographic evaluation. This form may cause an initial opinion based on B-mode sonography that may affect the sonoelastographic comment. Finally, the longer postprocessing time for thyroid stiffness index limits this kind of assessment until the process can be performed more rapidly.

In conclusion, we found that ultrasound elastography is an easy, noninvasive and rapid technique that can be routinely used in thyroid US scans to select cases for FNAC, decrease the number of unnecessary biopsies, and consequently decrease the hazards and costs. It can be an effective method in changing the clinical decisions regarding indeterminate thyroid nodules, as cases with an elasticity score of 4 and 5 are considered to be highly malignant so surgery can be advised without FNAC, while FNAC should be recommended in all cases of score 3 where malignancy cannot be excluded using ultrasound elastography criteria only. Nodules with a score less than 3, do not require further assessment with FNAC. However, future advances in image acquisition and reconstruction algorithms are required to improve the image quality and clinical usefulness of this technique.

Conflict of interest

The authors declare that there are no conflict of interests.

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