Original Research Article

Diagnostic accuracy of strain ultrasound elastography in differentiating benign and malignant thyroid nodules, taking histopathology as gold standard

Maham Fatima1, Shifa Younus2, Hamza Maqsood2*, Amna Younas2, Farah Mukhtar1, Mahnoor Fatima Shah1, Hassan Raza3, Saim Mazhar2, Muhammad Qasim2, Muhammad Shahzeb Khan Khakwani2

1Department of Radiology, 2Department of Medicine, Nishtar Hospital, Multan, Punjab, Pakistan

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*Correspondence:
Dr. Hamza Maqsood,
E-mail: hamzamaqsood381@gmail.com

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Abstract

Background: Elastography is a method recently being used in the evaluation of thyroid nodules by comparing tissue elasticity. Strain and shear wave elastography are two types of elastography still being used in clinical practice. Two kinds of elasticity can be assessed by strain elastography. First, colors around and within the nodules are evaluated and visually scored according to the 4-5 scale scoring systems. The aim of this study was to determine the diagnostic accuracy of strain ultrasound elastography in differentiation between benign and malignant thyroid nodules, taking histopathology as gold standard

Methods: Total of 101 patients with palpable thyroid nodule of any size of age 30-70 years of either gender were included. Patients with previous thyroid surgery and already proven histopathology were excluded. Strain ultrasound elastography was performed in every patient by using a highresolution unit with a linear array probe centred at 7.5 MHz. Strain ultrasound elastography was performed in every patient by a consultant radiologist in the presence of researcher and benign or malignant thyroid nodules was noted. Strain USG elastography findings were compared with histopathology report.

Results: All the patients were subjected to strain ultrasound elastography. USG supported the diagnosis of malignant thyroid nodules in all 52 patients. Histopathology confirmed malignant thyroid nodules in 47 (true positive) cases where as 5 (false positive) had no malignant lesion on histopathology. In USG negative patients, 46 were true negative while 3 were false negative. Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of strain ultrasound elastography in differentiation between benign and malignant thyroid nodules, taking histopathology as gold standard is 94.0%, 90.20%, 90.38%, 93.88% and 92.08% respectively.

Conclusions: According to this study, strain ultrasound elastography is the non-invasive modality of choice with high diagnostic accuracy in diagnosing malignant thyroid nodules.

Keywords: Thyroid cancer, Ultrasound elastography, Sensitivity, Specificity

Introduction

Thyroid nodules are reported to be found in 33% of unselected adults between the age of 18 and 65 years and in 50% of the population of over 65 years of age.1 Although the majority of the thyroid nodules are benign, malignancy has a prevalence of 5-15%.2 After a thyroid nodule is found during a physical examination, a referral to an endocrinologist, or a thyroidologist may occur. Most commonly an ultrasound is performed to confirm
the presence of a nodule, and assess the status of the whole gland. Measurement of thyroid stimulating hormone and anti-thyroid antibodies will help decide if there is a functional thyroid disease such as Hashimoto's thyroiditis present, a known cause of a benign nodular goiter. Measurement of calcitonin is necessary to exclude the presence of medullary thyroid cancer. Finally, to achieve a definitive diagnosis before deciding on treatment, a fine needle aspiration cytology test is usually performed and reported according to the Bethesda system.

Ultrasound (US) is accurate in the detection of thyroid nodules, but it has a relatively low diagnostic performance for the differentiation between benign and malignant nodules. US sensitivity and specificity in characterizing thyroid nodules vary considerably from study to study and range between 52 and 97% and 26.6 and 83%, respectively. According to the American thyroid association guidelines, no single US feature or combination of features is adequately sensitive or specific to identify all malignant nodules.

Elastography is a method recently being used in the evaluation of thyroid nodules by comparing tissue elasticity. Strain and shear wave elastography (SWE) are two types of elastography still being used in clinical practice. Two kinds of elasticity can be assessed by strain elastography. First, colors around and within the nodules are evaluated and visually scored according to the 4–5 scale scoring systems. Second, regions of interest are specified as the target region and the adjacent reference region. Later, elastography calculates strain ratio automatically. Higher strain ratio leads to a high probability of malignancy. In a study, the prevalence of malignant thyroid nodule was found to be 40.65% and sensitivity and specificity of strain ultrasound elastography as 88.0% and 93.0% respectively in differentiating benign and malignant thyroid nodules. Another study has shown that strain elastography had the highest sensitivity of 100.0% and specificity of 80.2% in the differentiation between benign and malignant thyroid nodules.

The available literature on diagnostic accuracy of strain ultrasound elastography in differentiation between benign and malignant thyroid nodules has shown variable results and also no local statistics available on this, so we did this study to determine the diagnostic accuracy of strain ultrasound elastography in differentiation between benign and malignant thyroid nodules. As biopsy is gold standard to determine the exact nature of thyroid nodules, however it is invasive and has risk of bleeding, so there is need for reliable, non-invasive technique that can accurately assess the nature of thyroid nodule. The results of our study will provide our population with a non-invasive, cheap and easily available imaging modality for differentiating benign and malignant thyroid nodule and thus selection of timely and proper treatment option in order to reduce the morbidity and mortality of the disease as well as the purely invasive diagnostic biopsies.

METHODS

Study design and setting

A descriptive, cross-sectional study was carried out from October 2019 to June 2020 at radiology department of Nishtar Hospital, Multan. Ethical issues were addressed according to institutional review board. All the participants were informed about the targets of the research and the methods of the study. All procedures were performed only with the consent of the participants, and all information was used solely for this research.

Inclusion criteria

Patients with 30-70 years of age, patients with palpable thyroid nodule of any size (on clinical examination) and with duration of disease >3 months were included in the study.

Exclusion criteria

Patients with previous history of thyroid surgery and patients with already proven histopathology (assessed on medical record) were excluded from the study.

Procedure and data analysis

Sample size of 101 cases was calculated with 95% confidence level, 10% desired precision for sensitivity and 6.5% for specificity, prevalence of malignant thyroid nodule as 40.65% and sensitivity and specificity of strain ultrasound elastography as 88.0% and 93.0% respectively in differentiating benign and malignant thyroid nodules. Non-probability, consecutive sampling was done.

After taking informed consent, strain ultrasound elastography was performed on every patient by using a high-resolution unit with a linear array probe centred at 7.5 MHz. Strain ultrasound elastography was performed in every patient by a consultant radiologist (with at least 3 years post-fellowship experience) in the presence of researcher and benign or malignant thyroid nodules was noted as per-operational definition. Strain USG elastography findings were compared with histopathology report which was performed in the concerned ward and sent to the institutional pathology laboratory. All this data (age, gender, duration of disease, size of nodule, benign and malignant thyroid nodule) was recorded on a specially designed proforma. The data was entered and analysed on SPSS 20. Mean and standard deviation were calculated for age, duration of disease and size of nodule. Frequency and percentage were presented for gender, benign and malignant thyroid nodule on strain USG and histopathology. 2x2 contingency table was used to calculate sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy.
of strain ultrasound elastography in differentiating benign and malignant thyroid nodule, taking histopathology as gold standard. Effect modifiers like age, gender, duration of disease and size of nodule were controlled by stratification. Post - stratification diagnostic accuracy was calculated.

RESULTS

Age range in this study was from 30-70 years with mean age of 42.07±7.76 years. Majority of the patients 92 (91.09%) were between 30 to 50 years of age. Out of these 101 patients, 49 (48.51%) were female and 52 (51.49%) were males with female to male ratio of 1:1 (Figure 1). Mean duration of disease was 10.06±3.32 months. Mean size of nodule was 4.68±1.49 cm. All the patients were subjected to strain ultrasound elastography. USG supported the diagnosis of malignant thyroid nodules in all 52 patients. Histopathology confirmed malignant thyroid nodules in 47 (true positive) cases where as 5 (false positive) had no malignant lesion on histopathology. In USG negative patients, 46 were true negative while 3 were false negative (Table 1). Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of strain ultrasound elastography in differentiation between benign and malignant thyroid nodules, taking histopathology as gold standard is 94.0%, 90.20%, 90.38%, 93.88% and 92.08% respectively.

Table 1: Diagnostic accuracy of strain ultrasound elastography in differentiation between benign and malignant thyroid nodules, taking histopathology as gold standard.

<table>
<thead>
<tr>
<th></th>
<th>Positive result on histopathology</th>
<th>Negative result on histopathology</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive on strain</td>
<td>47 (true positive)</td>
<td>5 (false positive)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ultrasonography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative on strain</td>
<td>3 (false negative)</td>
<td>46 (true negative)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ultrasonography</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stratification of diagnostic accuracy with respect to duration of disease and size of nodule is depicted in Table 2-3.

![Figure 1: Gender wise distribution of study population.](image)

DISCUSSION

Thyroid nodules are widely encountered in population, and they are usually benign. Its prevalence rates differ according to the population and the method used. It has also been reported that the prevalence of thyroid nodules is gradually increasing. The risk factors for thyroid nodules include female gender, advanced age, iodine deficiency, and previous head and neck radiation. The prevalence of thyroid nodules has been reported to be detected 2-6% by palpation, 19-35% by ultrasonography (US), and 8-65% in autopsy data.

Although palpation has an important place in the diagnosis of thyroid nodules during physical examination, ultrasonography is the most accurate and cost effective method. Fine-needle aspiration biopsy (FNAB) is mandatory in the preoperative diagnosis of thyroid nodules and in distinguishing benign from malignant nodules. High-resolution thyroid ultrasonography and real-time elastography are adjuvant tools to be benefited from in order to decide whether the patient in question should undergo surgery, especially if the patient has indeterminate or nondiagnostic cytology.

Elastography is a method recently being used in the evaluation of thyroid nodules by comparing tissue elasticity. Strain and shear-wave elastography (SWE) are two types of elastography still being used in clinical practice. Two kinds of elasticity can be assessed by strain elastography. First, colours around and within the nodules are evaluated and visually scored according to the 4-5 scale scoring systems. Second, regions of interest are specified as the target region and the adjacent reference region. Later, elastograph calculates strain ratio automatically. Higher strain ratio leads to a high probability of malignancy. A quantitative elastic value can be obtained by SWE depending on the acoustic pulse of an ultrasound probe, which stimulates tissues; accordingly, a real-time elastogram can be provided. The supersonic shear wave and acoustic radiation force impulse methods are used for the clinical assessment of thyroid nodules.

In our study all the patients were subjected to strain ultrasound elastography. USG supported the diagnosis of malignant thyroid nodules in all 52 patients. Histopathology confirmed malignant thyroid nodules in 47 (true positive) cases where as 5 (false positive) had no malignant lesion on histopathology. In USG negative...
patients, 46 were true negative while 3 were false negative. Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of strain ultrasound elastography in differentiation between benign and malignant thyroid nodules, taking histopathology as gold standard is 94.0%, 90.20%, 90.38%, 93.88% and 92.08% respectively. In a study, the prevalence of malignant thyroid nodule was found to be 40.65% and sensitivity and specificity of strain ultrasound elastography as 88.0% and 93.0% respectively in differentiating benign and malignant thyroid nodules. 9 Another study has shown that strain elastography had the highest sensitivity of 100.0% and specificity of 80.2% in the differentiation between benign and malignant thyroid nodules. 10

**Table 2: Stratification of diagnostic accuracy with respect to duration of disease ≤12 months (N=79) and >12 months (N=22).**

<table>
<thead>
<tr>
<th>Duration of disease ≤12 months</th>
<th>Positive result on histopathology</th>
<th>Negative result on histopathology</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive on strain ultrasonography</td>
<td>37 (true positive)</td>
<td>4 (false positive)</td>
<td>0.001</td>
</tr>
<tr>
<td>Negative on strain ultrasonography</td>
<td>2 (false negative)</td>
<td>36 (true negative)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of disease &gt;12 months</th>
<th>Positive result on histopathology</th>
<th>Negative result on histopathology</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive on strain ultrasonography</td>
<td>10 (true positive)</td>
<td>1 (false positive)</td>
<td>0.001</td>
</tr>
<tr>
<td>Negative on strain ultrasonography</td>
<td>1 (false negative)</td>
<td>10 (true negative)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Duration of disease ≤12 months; sensitivity: 94.87%, Specificity: 90.0%, PPV: 90.24%, NPV: 94.74%, diagnostic accuracy: 92.41%. Duration of disease >12 months; sensitivity: 90.91%, specificity: 90.91%, PPV: 90.91%, NPV: 90.91%, diagnostic accuracy: 90.91%.

**Table 3: Stratification of diagnostic accuracy with respect to size of nodule ≤5 cm (N=70) and >5 cm (N=31).**

<table>
<thead>
<tr>
<th>Size of nodule ≤5 cm</th>
<th>Positive result on histopathology</th>
<th>Negative result on histopathology</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive on strain ultrasonography</td>
<td>29 (true positive)</td>
<td>4 (false positive)</td>
<td>0.001</td>
</tr>
<tr>
<td>Negative on strain ultrasonography</td>
<td>3 (false negative)</td>
<td>34 (true negative)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size of nodule &gt;5 cm</th>
<th>Positive result on histopathology</th>
<th>Negative result on histopathology</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive on strain ultrasonography</td>
<td>18 (true positive)</td>
<td>1 (false positive)</td>
<td>0.001</td>
</tr>
<tr>
<td>Negative on strain ultrasonography</td>
<td>0 (false negative)</td>
<td>12 (true negative)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Size of nodule ≤5 cm; sensitivity: 90.63%, Specificity: 89.47%, PPV: 87.88%, NPV: 91.89%, diagnostic accuracy: 90.0%. Size of nodule >5 cm; sensitivity: 100.0%, specificity: 92.31%, PPV: 94.74%, NPV: 100.0%, diagnostic accuracy: 96.77%.

In 2010 a meta-analysis of 8 studies including a total of 639 thyroid nodules resulted in encouraging results. An overall mean sensitivity of 92% (confidence interval 88-96%) and mean specificity of 90% (confidence interval 85-95%) were shown with a significant heterogeneity found for specificity in the different studies. 15 However, the first encouraging results were challenged by a large retrospective study of Moon et al with 703 nodules (217 malignant). 16 SE was assessed with both Asteria and Rago scoring criteria, but the results showed inferior performance of elastography; sensitivity 65.4% and negative predictive value (NPV) 79.1%, compared with gray-scale US features in combination (sensitivity 91.7% and NPV 94.7%), so the authors concluded that SE was not useful in recommending FNAB. Similarly, discouraging results are reported in another study of 2012 with 237 thyroid nodules (58 malignant) that reported lower performance of RTE in comparison with gray-scale US. 17

On the other hand, in 2013, however, the study group of Azizi et al in a prospective study using four-grade elasticity score in the evaluation of 912 nodules resulted in positive predictive value (PPV) of 36.1%, which was slightly higher than that of microcalcifications (35.9%) and significantly greater compared with hypo-echogenicity (13.6%) and isthmus location (16.9%). The negative predictive value (NPV) of elasticity score was 97.2%, which was better than any other predictor for malignancy. This study involved the greatest number of nodules ever to be systematically studied with SE and furthermore it had no patient selection bias unlike the two above mentioned studies. 18 Ko et al evaluated the effect of physician’s experience in distinguishing malignant thyroid nodules from benign nodules using elastography and reported that experienced physicians had superior specificity compared to inexperienced physicians. 19 In another study, for interobserver agreement, Cantisani et al reported the highest Cohen’s kappa coefficient for the strain ratio measurements (0.95) and the lowest Cohen's kappa coefficient for the echogenicity score (0.83). 20 In their study conducted with three independent operators, Ragazzoni et al found a good agreement among the operators (kappa test: 0.64, p<0.0001). In the present study, the agreement between two examiners’ scoring was almost perfect compared to the final scoring (kappa
values 0.835 for the first examiner and 0.815 for the second examiner).21

Ragazzoni et al conducted a study with 132 nodules (92 benign and 40 malignant) using elastography and reported 77 out of 92 benign nodules were categorized as score 1 or 2 and 34 out of 40 malignant nodules were categorized as score 3 or 4 (sensitivity 85%, specificity 83.7%, PPV 69.3%, and NPV 92.7%).21 Asteria et al evaluated 17 malignant and 69 benign lesions and found the sensitivity, specificity, PPV, NPV, and accuracy of elastography to be 94.1%, 81%, 55.2%, 98.2%, and 83.7%, respectively.22 Ferrari et al evaluated 23 thyroid nodules and reported that 78% of benign nodules were patterns 1-2 and 88% of malignant nodules were patterns 3-4. In the same study, the sensitivity, specificity, PPV, NPV, and diagnostic accuracy of elastography were determined to be 88%, 78%, 72%, 91%, and 82%, respectively.23 Moreover, Cantisani et al prospectively evaluated 97 patients and found the sensitivity and specificity of elastography to be 97.3% and 91.7%, respectively, and reported that the lesions with strain ratio ≥2 were quite likely in malignant nature.24

In another study by Cantisani et al they evaluated 89 benign and 58 malignant cases who underwent thyroidectomy and found the sensitivity and specificity to be 93% and 89%, respectively, when the cutoff value for elastography score was considered to be 2. According to the result of that particular study, it was reported that elastography provided more accurate findings compared to US and color Doppler US.25 Shweel and Mansour found the sensitivity, specificity, PPV, NPV, and accuracy of elastography to be 75.4%, 85.5%, 71.4%, 90.5%, and 86.7%, respectively, and reported that diagnostic performance of elastography increased when it was used together with high-resolution US.26

Another meta-analysis published in 2013 included 24 studies with 2624 patients and 3531 thyroid nodules (927 malignant and 2604 benign). Their statistical analysis yielded diagnostic performance measures which were better for SE than for US features. The sensitivities and specificities were, respectively, as follows: elasticity score, 82% and 82%; strain ratio, 89% and 82%; hypechoicogenicity, 78% and 55%; microcalcifications, 50% and 80%; irregular margins, 66% and 81%; absent halo sign, 56% and 57%; nodule vertical development, 46% and 77%; and intranodular vascularization, 40% and 61%. They concluded that USE increased US accuracy.27

In another meta-analysis performed by Ghajarzadeh et al 12 studies, which evaluated 1180 thyroid nodules, were systematically reviewed, and diagnostic accuracy of sonoelastography in detecting malignant nodules was investigated. They concluded that the highest sensitivity was achieved by a threshold elasticity score of between 1 and 2 as 98.3% (95% CI, 96.2%-99.5%). They also reported that it was not necessary for the patients with elasticity score of 1 to undergo further invasive examinations.28 Akcay et al evaluated 110 nodules by stiffness score using US elastography and found the sensitivity, specificity, PPV, and NPV to be 100%, 95%, 40%, and 100%, respectively, when the cut off value for malignancy was considered to be score 4; they recommended biopsy for all score 4 nodules but not for score 1.29

In a study, fifty patients with 73 indeterminate thyroid nodules were included, 16 nodules were malignant and 57 were benign. On US elastography, all 57 nodules diagnosed as benign had a score of 1-3, while 15 of 16 (93.75%) diagnosed as carcinoma had a score of 4-5, with 93.3% sensitivity, 100% specificity and 97.8% accuracy. Combined US findings with elastography revealed that hypechoegenicity score 4-5 was most predictive of malignancy with sensitivity 80%, specificity 100%; and accuracy 93.4%. The strain ratio cut off value for malignant nodules was determined as 2.3. Five nodules out of sixteen had SR between 2.31 and 4 (sensitivity 96% and specificity 83%).30

Asari et al reported that the real-time USE is based upon the principle that the softer parts of tissues deform more rapidly than the harder parts under compression, thereby allowing objective determination of tissue maximum diameter with an indeterminate result on conventional ultrasound. An elasticity score of 4-5 was highly predictive of malignancy, with a sensitivity of 90.63%, a specificity of 89.47% and an accuracy of 90.20%.31 In the study of Asteria et al they reported that the sensitivity, specificity, PPV and NPV of the USE for thyroid cancer diagnosis were 94.1%, 81%, 55.2% and 98.2%, respectively while the accuracy was 83.7%.32

CONCLUSION

This study concluded that strain ultrasound elastography is the noninvasive modality of choice with high diagnostic accuracy in diagnosing malignant thyroid nodules, and has not only dramatically improved our ability of diagnosing malignant thyroid nodules preoperatively but also helps the surgeons for proper decision making. So, we recommend that strain ultrasound elastography should be done routinely in all thyroid lesions for accurate diagnosis of malignant thyroid nodules preoperatively and opting proper surgical approach.

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Ethical approval: The study was approved by the Institutional Ethics Committee
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