Efficacy of Sonoelastography in Distinguishing Benign from Malignant Breast Masses

Adile Balçık1, Ahmet Veysel Polat2, İlkay Koray Bayrak2, Ayfer Kamalı Polat3
1Clinic of Radiology, Afyonkarahisar State Hospital, Afyonkarahisar, Turkey
2Department of Radiology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey
3Department of General Surgery, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey

ABSTRACT
Objective: The study aimed to evaluate the influence of sonoelastographic strain ratio in distinguishing benign from malignant breast masses.

Materials and Methods: Patients who were referred for diagnostic biopsy of a breast mass were examined by ultrasound and sonoelastography prior to percutaneous biopsy. Sonoelastography was performed twice by the same observer in the same session. The strain ratios (SR) were calculated for both measurements as well as the mean strain ratio. Results were compared with histopathologic findings. For each strain ratio, a threshold value was determined using a ROC analysis for the differentiation of benign and malignant masses.

Results: After histopathological examination of 135 mass lesions in 132 female patients (mean age 48±12 years), 65 masses were diagnosed as benign and 70 as malignant. According to the Tsukuba classification with 5 scores; 44 of 65 benign masses had scores of either 1 or 2 while 56 of 70 malignant lesions had scores of either 4 or 5. No benign lesion was classified as score 5, and no malignant lesion as score 1. The mean cut-off in the two ROC measurements in distinguishing benign from malignant lesions was calculated as 4.52. When a threshold value of 4.52 was used for the mean strain ratio: the sensitivity, specificity, PPV, NPV, and accuracy rates were determined as 85.5%, 84.8%, 85.5%, 84.8% and 85.2%, respectively.

Conclusion: The threshold value for strain ratio in the differentiation of benign and malignant masses was detected as 4.52, and a significant intra-observer difference was not observed in this study. The diagnostic value of sonoelastography in distinguishing benign from malignant breast masses was higher in comparison to conventional ultrasound.

Keywords: Breast neoplasm, ultrasound, sonoelastography

Introduction
Breast ultrasound (US) is a non-invasive, inexpensive modality without ionizing radiation. It is useful in the radiologic differentiation of solid-cystic lesions detected on mammography, especially in dense breasts. Although ultrasound has a high diagnostic accuracy, it has some limitations in distinguishing benign from malignant tumors. The lesions that cannot be differentiated as either benign or malignant by ultrasound require biopsy in order to obtain histopathologic diagnosis, 60-95% of which are diagnosed as benign. This leads to unnecessary disruption of patient comfort, patient anxiety and financial loss. That is why, noninvasive methods that can increase the sensitivity and specificity of mammography and ultrasound thereby reduce unnecessary biopsies of benign lesions are required (1-3).

Methods to improve the diagnostic specificity and accuracy of ultrasound without affecting its sensitivity in the evaluation of breast lesions have been investigated. Sonoelastography is a non-invasive ultrasound technique determining the stiffness of lesions and the probability of malignancy for that lesion. Malignant tissues are generally harder than benign tissues due to the diffuse desmoplastic reaction they contain. This method evaluates compressibility of the length between two specified points. Malignant lesions are usually harder in structure that represent as non-compressible lesions, while normal tissues with soft character and benign nature are compressible. This distance changes that represent compressibility is called “elastography” (4-7).

The elasticity of the breast lesion is compared with that of the normal surrounding tissue for breast sonoelastography, and is scored from 1 to 5. Since this scoring is a subjective method, an index known as the “strain ratio” is defined for semiquantitative determination of tissue stiffness. In addition to these, it has been determined that the fat tissue in the breast, normal glandular tissue, fibrous tissue, ductal carcinoma in situ and invasive ductal carcinoma all have different elastic modules and strain ratios (8).
The aim of this study was to evaluate the contribution of elastographic strain ratios in the distinction between benign and malignant breast masses.

Material and Methods

Our study was conducted at Ondokuz Mayis University Faculty of Medicine Department of Radiology between October 2011–July 2013. A faculty ethics committee approval was obtained for this prospective study as well as informed consents from all participants. Patients who were referred for diagnostic biopsy of a breast mass were prospectively evaluated. The same physician performed the conventional ultrasound and sonoelastography evaluations prior to biopsy in all patients. The sonoelastography examination was held twice in the same session by the same radiologist and strain ratios were calculated for each study in order to evaluate intra observer agreement. Conventional ultrasound findings, both strain ratios and the mean strain ratio were recorded and compared with histopathologic results.

Ultrasound examinations were performed in a fairly low lightning ultrasound room. Patients were examined in the supine position. The examination was performed by using a digital ultrasound elastography device (Aplio XG SSA-790, Toshiba Medical Systems Corporation, Otawara, Japan) equipped with real-time elastography software and a 8-MHz linear transducer.

Initially conventional ultrasound was performed in all patients to assess the size, shape, border characteristics, posterior acoustic features, echogenicity, internal structure, and the presence of calcification in the lesion; the images of these features were recorded and lesions were classified according to the ultrasound ‘breast imaging, report and data systems’ (BI-RADS) categories. According to BI-RADS categorization, the threshold for benign and malignant distinction was considered as BI-RADS 3-4.

Sonoelastography measurements were performed immediately after conventional ultrasound. The ultrasound transducer was placed on the breast mass in the supine position, parallel to the long axis of the mass. The operator placed sonoelastography box over the lesion to be evaluated after obtaining the complete ultrasonographic view of the breast lesion on the screen, and performed 5-6 consecutive compression-decompression frames in the anteroposterior direction. In eight lesions, the long axis of the mass was greater than the probe length therefore, the assessment was performed in a way to include the majority of the lesion and some normal adipose tissue. During the probe movement, grayscale ultrasound images of the mass were simultaneously visualized on the sonography screen. The ultrasound device automatically produced the sonoelastography images by comparing the two adjacent compression and relaxation frames that were obtained with continuous probe movement. The compression and relaxation curves were seen as curves above and below the base line on the elastography screen, respectively. The strain pattern in the resulting sonoelastography image was visually scored according to the Tsukuba scoring method defined by Itoh et al. (9) (Figure 1). Then, the strain ratio was calculated for the specified lesion. The strain ratio evaluation was made in the most appropriate relaxation curve with a sinusoidal shape. The strain ratio was obtained by comparing strain values of the lesion and normal tissue at a similar depth. The mean strain ratio was determined in the region of interest (ROI) that was depicted by the letter A placed over the mass. The ROI was drawn in a way that covered the entire lesion considering the areas with different firmness and presence of calcifications within the mass. In lesions that had a greater axis than the probe, the ROI was placed so that the mass could be covered almost entirely. Then, the letter B was placed in the adipose tissue adjacent to the ROI. The compression-decompression process and strain ratio calculation was repeated twice for each patient. Finally, the strain ratio that reflected mass stiffness was calculated by the following formula: Strain ratio = B / A (Figure 2).

All patients underwent ultrasound guided 14G tru-cut biopsy on the same day after sonoelastography examination. 142 patients with 145 mass lesions were evaluated with sonoelastography. Eight patients in whom the histopathologic examination results could not be obtained, and two patients with insufficient and unreliable histopathologic diagnoses (non-diagnostic) were excluded from the study. Overall, 135 solid lesions in 132 female patients formed the basis for the study group.

Statistical analysis

All statistical analyzes were performed with Statistical Package for the Social Sciences version 15.0 software package (SPSS, Inc.; Chicago, IL, USA). The quantitative data were compared by using the Student-t test and the qualitative data by the chi-square test. An ROC analysis was used to determine the optimal threshold value for strain ratio. Cross-table tests were performed to evaluate the diagnostic value of conventional ultrasound and sonoelastography by comparing their findings with the histopathologic results. Diagnostic sensitivity, specificity, positive predictive value, negative predictive value, and accuracy

Figure 1. a-e. According to the Tsukuba scoring system (a) ES-1 lesion coded entirely in green, indicates that the mass is soft (b) ES 2-mass coded in blue and green mosaic, indicates the heterogeneous distribution of soft-hard internal structure. c. ES3-mass is coded in blue in the center surrounded by green color, indicating that the central lesion is hard while has a softer outer structure (d) ES4-mass that is completely blue indicating that it is completely rigid and has a firm internal structure (e) ES5-blue coding on the mass and surrounding adjacent tissue covering an area larger than the size of the mass indicating rigid internal structure due to the desmoplastic reaction in both the mass and the surrounding soft tissue (9)
rates were calculated. The agreement between two strain ratios measured by the same person was evaluated by the concordance correlation coefficient statistics. The concordance of the two strain ratios in terms of differentiating malignancies was evaluated by the κ test statistic. According to Landis and Koch the kappa value:

<0 No agreement
0.0 - 0.20 Slight agreement
0.21 - 0.40 Fair agreement
0.41 - 0.60 Moderate agreement
0.61 - 0.80 Substantial agreement
0.81 - 1.00 Almost perfect agreement (10).

Quantitative data were expressed as (AO ± SD). A p value less than 0.05 was considered as statistically significant at the 95% confidence interval.

Results

The mean patient age was 48±12 years (range 16-82 years). One hundred thirty patients had one lesion each, one patient had 2, and one had 3 lesions yielding a total of 135 breast masses. The mean maximum diameter in the study group was 18±8 mm (range 6-50 mm), and the mean minimum diameter was 12±6 mm (range 3-40 mm).

Sonoelastography results

According to the Tsukuba scoring system consisting of five categories, 44 of 65 benign lesions were Score 1 or 2. On the other hand, 56 of the 70 malignant lesions had a score of 4 or 5. There were no benign lesions within Score 5 lesions, or no malignant lesions within those with Score 1 (Table 4).

The mean strain ratio in both measurements and the overall mean were 2.8±1.7, 3.07±1.8 and 2.9±1.7 for benign masses, and 8.4±4.2, 8.7±3.9 and 8.6±3.8 for malignant lesions, respectively (Figure 3, 4).

The mean strain ratios of malignant masses were significantly higher than benign masses in all three evaluations (p<0.0001).

Histopathology examination revealed 65 benign masses, while 70 were diagnosed as malignant (Table 1, 2).

Ultrasound findings were classified according to BI-RADS categorization. Since biopsy is not indicated for BI-RADS 2 lesions and only patients who underwent biopsy were included in our study, they were not represented in this study. Within BIRADS 3 lesions, 1 was diagnosed as malignant and one BI-RADS 5 lesion was diagnosed as benign (Table 3).

Table 2. Histopathology results of malignan

<table>
<thead>
<tr>
<th>Histopathology Result</th>
<th>Malignant (n=70)</th>
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<tbody>
<tr>
<td>Invasive ductal carcinoma</td>
<td>63 (88.6%)</td>
</tr>
<tr>
<td>Granulocytic sarcoma</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Invasive papillary carcinoma</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Malignant phyllodes tumor</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Breast carcinoma with neuroendocrine differentiation</td>
<td>1 (1.4%)</td>
</tr>
</tbody>
</table>

Table 3. Histopathologic results according to BI-RA

<table>
<thead>
<tr>
<th>BI-RADS 3</th>
<th>BI-RADS 4</th>
<th>BI-RADS 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>Malignant</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>51</td>
</tr>
</tbody>
</table>

BI-RADS: Breast imaging, report and data systems
For the first measurement, the threshold value in distinction between benign and malignant masses was found to be 4.60. When this threshold was used; the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were detected as 84.1%, 83.3%, 84.1% and 83.3%, respectively. The threshold value in distinction between benign and malignant masses was found to be 4.65 for the second measurement. When this threshold was used; the sensitivity, specificity, PPV and NPV were found as 83.8%, 83.6%, 83.8% and 83.6%, respectively. When the mean of the two measurements were taken, the threshold value in distinguishing between benign and malignant masses was found to be 4.52. This threshold value resulted in the sensitivity, specificity, PPV, NPV, and accuracy rates of 85.5%, 84.8%, 85.5%, 84.8% and 85.2%, respectively. When the ROC curves for these three values were considered together, the curves were found to be similar (Figure 5).

The $\kappa$ value for the two strain ratio measurements was 0.82, which showed an almost perfect agreement between the two strain ratio measurements in the distinction between benign and malignant lesions. The concordance correlation coefficient between the two measurements was determined as 0.87, with an almost perfect agreement (Figure 6).

The diagnostic accuracy rate of sonoelastography in predicting malignancy was found to be higher when evaluated according to BI-RADS categories. Although strain ratio and elasticity scoring with five categories showed similar accuracy rates, the strain ratio values were found to have a higher sensitivity (Table 5).

When the mean strain ratio values were determined, 10 false positive and 10 false negative results were detected. Six of the false positive results were detected in patients with fibroadenoma, 2 in fibrotic breast tissue, 1 in fibrocystic change and 1 in fat necrosis. Seven of the false-negative results were detected in patients with invasive ductal carcinoma, one in malignant phyllodes tumor, one in granulocytic sarcoma, and one in mucinous carcinoma.
The sensitivity was determined as 89.1% and the specificity as 50.5%.

Additional ultrasound as 98.2% and the specificity as 44.1%, while if conventional ultrasound. They determined the sensitivity of conventional ultrasound was higher while specificity was higher in the scoring system. Kumm et al. (21) studied 310 lesions in 288 patients according to the elastography scoring system with a threshold value 79% and negative predictive value 91%.

Discussion and Conclusions

The first and the most appropriate imaging method to assess the breast in women with breast-related symptoms is mammography (11). Ultrasound is the most commonly used method to complement mammography, malignancy can be detected with high sensitivity. However, the low specificity of this method is a significant problem. Thus, a biopsy is performed for lesions that cannot be differentiated between benign or malignant in order to obtain a histopathologic diagnosis. 50-60% of biopsied lesions are diagnosed as benign, leading to unnecessary disruption of patient comfort, anxiety and financial loss (12). Although MRI is a valuable method used in breast imaging, it is an expensive method for screening with low specificity (13, 14). Studies on a new ultrasound technique, sonoelastography, have been done in recent years in order to differentiate benign and malignant lesions of the breast in a non-invasive manner with higher sensitivity and specificity. The firmness of tissues can be displayed in real time with different color codes by sonoelastography, and a qualitative visual scoring can be performed. In qualitative sonoelastography, the elastography is shown in B-mode sonography with a color range between green (soft tissue) and blue (hard tissue). In addition, a strain ratio is calculated by using the obtained elasticity map, by dividing the strain value of the normal tissue to that of the lesion, thereby allowing a semiquantitative measure of the lesion’s stiffness (15-17).

Many studies reported a higher specificity in sonoelastography in contrast to a higher sensitivity in conventional ultrasound. In the study of 281 lesions in 267 patients, Sohn et al. (18) used the six-category malignancy scoring in order to evaluate the sensitivity and specificity of conventional ultrasound. They determined the sensitivity of conventional ultrasound as 98.2% and the specificity as 44.1%, while if conventional ultrasound and sonoelastography were used in conjunction the sensitivity was determined as 89.1% and the specificity as 50.5%.

In their study with 100 lesions in 100 patients, Cho et al. (19) detected the sensitivity as 100% and specificity as 33% with a cut-off value between conventional ultrasound BI-RADS categorization category 3 and category 4. In contrast, when the cut-off value for sonoelastography score of 2 and scored 3 were used, they determined the sensitivity as 82% and specificity as 84%.

In their study with 111 lesions in 111 patients, Itoh et al. (9) reported the sensitivity as 96.2% and specificity as 62.7%, with a cut-off value between conventional ultrasound BI-RADS categorization category 3 and category 4, while the sensitivity was 71.2%, and specificity was 96.6% with a cut-off value of BI-RADS category 4 and category 5. In contrast, when the cut-off value between sonoelastography scores 3 and 4 were used, they determined the sensitivity as 86.5% and specificity as 89.8% (9).

Okar Atabey et al. (20) evaluated 96 patients with 110 lesions by US elastography and used the 5 score system. For US elastography, the specificity was reported as 83%, sensitivity 89%, positive predictive value 79% and negative predictive value 91%.

In our study, when the threshold value for conventional ultrasound was accepted as BI-RADS 3 to 4, the sensitivity was found to be 98.5% and the specificity 56.2%. For sonoelastography, the selected threshold value was score 3, yielding a sensitivity of 80.0% and specificity of 90.8%. According to these values, in accordance with the literature, the sensitivity of conventional ultrasound was higher than that of sonoelastography, while the specificity of sonoelastography was higher as compared to US. However, selecting different threshold values changes sensitivity and specificity values.

Different threshold values were calculated in previous studies using strain ratio and in most of these studies, the sensitivity of strain ratio was found to be higher than the scoring system, while specificity was higher in the scoring system. Kumm et al. (21) studied 310 lesions in 288 patients according to the elastography scoring system with a threshold score between 2 and 3, and determined the sensitivity as 76% and specificity as 81%. In the same study, with a threshold of 4.5 for strain ratio, the sensitivity was reported as 79%, and specificity as 76%. Based on these values, it was concluded that the sensitivity of strain ratio was higher while specificity was higher in the scoring system (21). Parajuly et al. (22) studied 342 lesions in 325 patients according to the elastography scoring system with a threshold score between 3 and 4, they found the sensitivity as 77.7% and specificity as 96.2%. In the same study, with a threshold of 3.54 for strain ratio, the sensitivity was reported as 94.5%, and specificity as 94.3%. Stachs et al. (23) studied 224 lesions in 215

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPD (%)</th>
<th>NPD (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI-RADS (for category 4-5)</td>
<td>98.5</td>
<td>56.2</td>
<td>71.1</td>
<td>97.2</td>
<td>77.7</td>
</tr>
<tr>
<td>Elasticity Score (for score 4-5)</td>
<td>80.0</td>
<td>90.8</td>
<td>90.3</td>
<td>80.8</td>
<td>85.2</td>
</tr>
<tr>
<td>Mean strain ratio</td>
<td>85.5</td>
<td>84.8</td>
<td>85.5</td>
<td>84.8</td>
<td>85.2</td>
</tr>
</tbody>
</table>

Table 5. Comparison of conventional ultrasound and sonoelastography values

This result suggested that the sonoelastography scoring system is a method that increased the specificity of conventional ultrasound (18).
patients according to the elastography scoring system with a threshold score between 3 and 4, they found the sensitivity as 87.9% and specificity as 73.1%; while with a threshold of 2 for strain ratio, the sensitivity was reported as 90.7%, and specificity as 58.2%. When Yaştu et al. (24) evaluated 76 lesions of 76 patients, with a cut-off value of 4.0 they reported the sensitivity as 83.3%, specificity 76.9%, positive predictive value 62.3%, and negative predictive value as 90.7%. When the strain pattern cut-off was accepted as score 4 and 5, the sensitivity was 42.7%, specificity 94.2%, positive predictive value 77.2%, and negative predictive value was 78%. If conventional ultrasound findings were assessed in combination with elastographic strain ratio, the sensitivity was 87.5%, specificity 71.1%, positive predictive value 58.3%, and negative predictive value was 92.5% (24).

Various studies in the literature detected a threshold between 2 and 4.5. In a study on 201 lesions in 201 patients, Fischer et al. (25) adopted the strain ratio threshold as 2.27. Yerli et al. (16) evaluated 71 patients with 78 lesions, and the strain ratio threshold used in that study was 3.52. In our study, when the threshold value of 4.52 was used for sonoelastography strain ratio measurements, the sensitivity was 85.5%, specificity 84.8%, positive predictive value 85.5%, negative predictive value 84.8% and the accuracy rate was 85.2%. According to these values, similar to the literature, the specificity of sonoelastography scoring system was higher than that of the strain ratio, while the sensitivity of strain ratio was found to be higher than that of the scoring system.

In the study on interobserver compliance by Yoon et al. (26), 53 patients with 65 lesions were evaluated. The compliance according to elasticity score was reported as ρ=0.46, and it was shown to increase to ρ=0.79 when the strain ratio and elasticity score were evaluated in combination (26). In our study, interobserver assessment was not performed but intraobserver agreement of measurements performed by the same person was assessed. The ρ value was detected as 0.82 revealing an almost perfect agreement.

Ten false negative results were detected in our study. The strain ratio of the six invasive ductal carcinomas with false negative results was equal to or greater than 3.5. One of the false-negative results was a mucinous carcinoma that was previously reported to be soft in consistency (27). The size of the granulocytic sarcoma patient with a false negative result was 5 cm, and it is known that as the size increases the feasibility and accuracy of elastography decreases, additionally that lesion contained necrotic areas on pathologic examination. Two of the false positive diagnoses were pathologically diagnosed as fibrotic breast tissue, this could be due to the hardness caused by fibrosis. Similarly, the six fibroadenomas with false positive results could have been caused by the excess stromal fibrotic component of some fibroadenomas. In addition, five fibroadenoma patients with false-positive results were over 40 years of age, and the cause of false-positive results in these patients may be the presence of calcifications that cannot be displayed by ultrasound (27, 28).

The lack of diversity of malignant lesions due to the small number of lesions is a limitation of our study. In addition, lack of interobserver evaluation creates another limitation.

According to our study, although the sensitivity of conventional ultrasound was higher, the specificity of sonoelastography in both the scoring system and the strain ratio were significantly higher. These results imply that sonoelastography is a simple, noninvasive and rapid diagnostic method that can provide a diagnostic contribution to conventional ultrasound by increasing specificity. It also may help in classification of BI-RADS 3 solid mass lesions as either BI-RADS 2 or 4. This might in turn reduce the rate of unnecessary biopsies, reduce anxiety in patients and may contribute to lowering biopsy costs. Sonoelastography is not a method to replace conventional breast ultrasound for detecting breast cancer, but may complement conventional breast US by increasing its diagnostic power.

**Ethics Committee Approval:** Ethics committee approval was received for this study.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.


**Conflict of Interest:** No conflict of interest was declared by the authors.

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Balçık et al. Sonoelastography in Breast Masses


