Real-time tissue elastography combined with BIRADS-US classification system for improving breast lesion evaluation

Fatma Zeinhom Moukhtar a, Amal Amin Abu ElMaati b,*

a Department of Radio Diagnosis, Cairo University, Egypt
b Department of Radio Diagnosis, Ain Shams University, Egypt

Received 6 May 2014; accepted 14 May 2014
Available online 14 June 2014

Abstract  Purpose: The purpose of this study was to establish the correlation of prospectively interpreted ultrasound elastography (USE) results with American College of Radiology Breast Imaging Reporting and Data System (BIRADS) assessment and pathologic diagnoses of sono-graphically visible breast masses and to determine whether USE can improve distinction of benign and malignant lesions.

Patients and methods: Between April 2012 and January 2014, sonoelastography of focal breast lesions was carried out in 410 patients with subsequent histological confirmation. We present data focusing on the sensitivity (SE), specificity (SP) and the positive (PPV) and negative predictive value (NPV) of sonoelastography. In addition we performed an analysis of the diagnostic performance, expressed by the pretest and posttest probability of disease (POD), in BI-RADS-US 3 or 4 lesions as these categories can imply both malignant and benign lesions and a more precise prediction would be a preferable aim.

Results: Sonoelastography demonstrated an improved SP (89.5%) and an excellent PPV (86.8%) compared to B-mode ultrasound (76.1% and 77.2%). Especially in dense breasts ACR III–IV, the SP was even higher (92.8%). In BI-RADS-US 3 lesions, a suspicious elastogram significantly modiﬁed the POD from 8.3% to a posttest POD of 45.5%. In BI-RADS-US 4 lesions, we found a pre-test POD of 56.6%. The posttest POD changed signiﬁcantly to 24.2% with a normal elastogram.
1. Introduction

Breast ultrasound elastography (USE) is a new technique of ultrasonic imaging that has shown effectiveness for detection of malignancy within breast lesions. USE provides information about the mechanical properties of tissue such as elasticity and strain and maps it into color images (1–4). Elasticity is the tendency of a tissue to resume the original size and shape; while strain is the level of change in size or shape in response to external compression (stress) (4). Each pixel of the image is assigned one of 256 specific colors and demonstrates the magnitude of tissue strain depending on physiological and pathological changes in breast structure (3,5). Harder tissues such as malignancy may result in decreased strain and are shown in blue, while softer tissues will reflect increased strain and are shown in red (3). Normal breast tissue which reflects average strain is shown in green (3). The color image is superimposed on B-mode ultrasound (US) image for a better recognition of the relationship between the strain distribution and the anatomical borders of the lesion (3,4,6). This information is further interpreted by evaluating the color pattern in a hypoechoic lesion (e.g., within lesion borders on US image), and in the surrounding breast tissue (3). A 1–5 scale elasticity score (ES) is assigned to each image based on its overall pattern, with the harder tissues (e.g. breast cancer) showing higher elasticity scores (3). Although characterization of solid breast masses by sonography has improved greatly since the early 1990s, specificity remains low, and to date a large number of breast biopsies result in benign diagnoses. Therefore, any additional sonographic information to improve lesion characterization would help increase specificity. Recently published studies have reported promising results using elasticity imaging, either in comparison with B-mode sonography or in conjunction with the B-mode findings (7–9).

A significant number of false positive and false-negative findings still occur (10). The consequence of a false-positive result in diagnostic imaging is the performance of an unnecessary biopsy. A false-negative result has an even more serious implication as the diagnosis of malignancy is delayed, with a potentially worse clinical outcome for the patient. In order to prevent excessive biopsies on the one hand and, in particular, to guarantee the highest level of patient safety on the other hand, diagnostic methods should be continuously refined.

Today, ultrasound (US) plays a decisive role in the diagnostic pathways, with high sensitivity and specificity (11). Despite technical advances, the most important step in bringing breast US to its current position was the introduction of the standardized BI-RADS-US-classification system by the American College of Radiology (ACR) (12).

The ACR BI-RADS-US lexicon provides various categories with predefined terminology to describe the dominant features of breast lesions accurately. According to the ACR, each lesion should be assigned a BI-RADS-US category ranging from BI-RADS-US 0 to BI-RADS-US 6 at the end of the diagnostic procedure (12). The distinct BI-RADS-US classification also implies what further clinical action should be taken: BI-RADS-US 4 lesions are possibly malignant and BI-RADS-US 5 lesions are probably malignant. Therefore, the appropriate consequence is a biopsy, usually under US guidance. Malignancy practically never occurs in BI-RADS-US 2 lesions, which are defined as benign findings. To our understanding, the group of BI-RADS-US 3 lesions remains a critical category. These findings are probably benign and short-term follow-ups are recommended. Nevertheless, malignancy is eventually diagnosed in about 3% of these lesions, resulting in a delayed diagnosis of cancer in a considerable number of patients (13). Therefore, a suitable predictor for malignancy in BI-RADS-US 3 lesions would be beneficial and of clinical relevance. Nowadays, newly developed US technologies may allow a better differentiation of benign and malignant masses (14).

The goal of our study was to determine the usefulness of USE in the evaluation of solid masses or indeterminate breast lesions in a clinical setting with pathology as the reference standard. Specifically, our aim was to establish the correlation of prospectively interpreted USE results with American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) assessment and pathologic diagnoses of sonographically visible breast masses and to determine whether USE can improve distinction of benign and malignant lesions, thereby increasing specificity and positive predictive value. The aim of our study is to focus on the application of USE for further characterization of lesions that are initially categorized as BI-RADS-US 3 or 4 as these categories can imply both malignant and benign lesions and a more precise prediction of a lesion’s malignancy status in these categories would be valuable.

2. Patients and methods

2.1. Patients

We performed 410 ultrasound examinations at a private center between April 2012 and January 2014. The patients were referred to the center due to specific diagnostic queries such as palpable breast lesions, pain, suspicious mammograms, breast cancer follow-up or intensified screening in high-risk populations. Patients, who presented a lesion in B-mode ultrasound that required the taking of a histological specimen, were considered to be suitable for the study, and additional elastographic examination was carried out. Finally the patients were scheduled to undergo ultrasound-guided core needle biopsy of the breast lesion. The age of the patients ranged from 18 to 72 years (mean, 42.6 years).
2.2. Ultrasound examinations and biopsy procedures

Ultrasound and elastography images were obtained by using a 6–14 MHz linear array transducer (Toshiba Aplio XG ultrasound machine). Real-time whole breast ultrasound examination was performed by an experienced radiologist (with 10 years of experience in breast imaging).

After the whole breast ultrasound examination, ultrasound and elastography were performed sequentially only at the lesion subjected to biopsy. In order to make the images comparable to each other and to perform the analysis, each elastogram had to include a complete sectional plane of the tumor as well as an adequate (more than approximately 50% of the area) amount of surrounding normal breast tissue.

Biopsy was performed by the same radiologist who performed the whole breast ultrasound examination. Local anesthesia (1% lidocaine) was routinely applied, and an automated gun (Pro-Mag 2.2, Manan Medical Products) and a 14-gauge True Cut needle with a 22-mm throw (SACN Biopsy Needle, Medical Device Technologies) were used. Informed patient consent was obtained for all biopsy procedures.

2.3. Real-time ultrasound elastography

Ultrasound elastography was performed using a freehand technique at the same time as ultrasound. Images were obtained by applying repetitive light compression at the skin above the targeted breast lesion. The probe was positioned perpendicular to the skin when applying pressure. The ultrasound scanner was equipped with an elastography unit, images were presented in a split-screen mode with the conventional images on the right, and the translucent color-scale elastography images were superimposed on the corresponding ultrasound image on the left. A square region of interest (ROI) was set for elastography acquisition; the superior margin was set to include subcutaneous fat, the inferior margin was set to include pectoral muscle, and the lateral margin was set to include more than 5 mm of breast parenchyma adjacent to the targeted lesion.

2.4. Image interpretation and data management

For each patient the B-mode ultrasound pictures were categorized according to the Breast Imaging Reporting and Data System criteria of the American College of Radiology (ACR BI-RADS-US) (12).

The elastograms were evaluated using the Tsukuba Elasticity Score, a 5-point strain scale partly corresponding to the BI-RADS classification (Fig. 1).

So far sensitivity and specificity are the highest when a score between 3 and 4 is established as the cut-off point for the malignancy (3). Therefore, lesions that are categorized as score 1 and score 2 are considered benign, and lesions categorized as score 4 and 5 are suspicious or highly suspicious for cancer. Lesions categorized as score 3 remain particularly unclear, but are more likely to be benign.

Score 1: strain appears in the entire hypoechoic area (the entire lesion is shown in green as in the surrounding normal breast).

Score 2: strain is not seen in part of the hypoechoic area (the lesion is shown as a mosaic of green and blue).

Score 3: strain appears only in the peripheral areas and not in the center of the hypoechoic area (the entire lesion appears in blue while the peripheral areas in green).

Score 4: no strain appears in the entire hypoechoic area (the entire lesion appears in blue).

Score 5: no strain appears either in the hypoechoic area or in surrounding areas (the lesion and surrounding areas are shown in blue).

2.5. Statistical analysis

We used the statistical software package SPSS 17.0 (Chicago, IL, USA). In order to assess the accuracy of real-time tissue elastography compared with the histological results. The diagnostic sensitivity, specificity and positive and negative predictive values as well as the pretest and posttest probability of disease were calculated based on the specimen histology as the gold standard using Fisher’s exact test. A separate analysis with respect to BI-RADS-US 3 and 4 tumors was performed.

3. Results

All 410 cases were histologically evaluated. Specimen histology demonstrated 196 malignant and 214 benign lesions. The histological results are summarized in Table 1. The average diameter of benign tumors was 15.8 ± 10.2 mm and 17.0 ± 9.2 mm of malignant tumors. The size difference was not significant (p > 0.05).

Using B-mode ultrasound for the 214 benign lesions, 163 were correctly identified, while 51 of these lesions were incorrectly classified as BI-RADS-US 4 or 5. Using USE, 192 of the 214 lesions were correctly classified. Regarding the malignant lesions, B-mode ultrasound yielded a correct classification of BI-RADS-US 4 or 5 in 186 of 196 cases. USE identified 146 lesions as malignant, but the remaining 50 lesions showed a normal elastogram.

The resulting sensitivity for conventional B-mode ultrasound was 95.0% and significantly higher than the sensitivity for USE that was 81.2%. Regarding the specificity, USE yielded the best result with 89.5%, which was significantly higher than the specificity in B-mode ultrasound (76.1%). The positive predictive value was high for USE (86.8%) and thus significantly higher than in conventional ultrasound, which showed a positive predictive value of 77.2%. B-mode ultrasound had the best negative predictive value of 94.7%, which was significantly higher than the negative predictive value of USE (84.8%). The results are summarized in Table 2.

3.1. Impact of evaluating BI-RADS-US 3 lesions with sonoelastography

Regarding the 95 lesions that were classified BI-RADS-US 3 in conventional ultrasound, we obtained the following results:

The pretest probability of disease in these cases was 8.3% and rose significantly to 45.5% with an abnormal elastogram (Tsukuba Elasticity Score 4 or 5). The posttest probability of disease with a normal elastogram (Tsukuba Elasticity Score 1 to 3) was only 3.1%, although this difference was not significant. The results are summarized in Table 3.
3.2. Impact of evaluating BI-RADS-US 4 lesions with sonoelastography

We performed the identical test as for the BI-RADS-US 3 lesions with respect to the BI-RADS-US 4 lesions (n = 112). For these lesions we found an initial probability of disease of 56.6%, which rose significantly to 81.5% after a positive test, meaning a suspicious elastogram (Tsukuba Elasticity Score 4 or 5). The posttest probability of disease with a normal elastogram (Tsukuba Elasticity Score 1–3) was 24.2% and therefore significantly lower. The results are summarized in Table 4.

3.3. Evaluating the accuracy of sonoelastography with respect to the density of the breast

We found no significant differences regarding the sensitivity and the positive predictive value, which were 84.2% and 89.6% in dense breasts ACR III-IV and 84.4% and 91.0% in less dense breasts ACR I-II.

There was a trend toward a higher specificity in dense breasts (92.8%) compared with ACR I-II breasts (82.7%) although this difference was not significant. The negative predictive value was significantly higher in dense breasts (88.8%) than in less dense breasts (72.0%). The results are summarized in Table 5.

Five case examples are presented. Fig. 2 shows a partially mottled low echo on USG lesion with TES of 4. Biopsy

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Table 1  Final pathologic diagnoses in 410 breast lesions.

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Malignant lesions</td>
<td>(196)</td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>136</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>33</td>
</tr>
<tr>
<td>Other invasive carcinoma</td>
<td>20</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>7</td>
</tr>
<tr>
<td>Benign lesions</td>
<td>(214)</td>
</tr>
<tr>
<td>Cyst</td>
<td>62</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>60</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>21</td>
</tr>
<tr>
<td>Fibrocystic mastopathy</td>
<td>22</td>
</tr>
<tr>
<td>Mastitis</td>
<td>8</td>
</tr>
<tr>
<td>Papilloma</td>
<td>4</td>
</tr>
<tr>
<td>Other benign</td>
<td>37</td>
</tr>
</tbody>
</table>

Table 2  Comparison of sensitivity, specificity, positive (PPV) and negative predictive value (NPV) for B-mode ultrasound in the differentiation of benign lesions from malignant breast cancer. 95% confidence interval in brackets.

<table>
<thead>
<tr>
<th></th>
<th>B-mode ultrasound</th>
<th>Sonoelastography</th>
</tr>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>95.0 (92.0–97.0)</td>
<td>81.2 (76.7–85.1)</td>
</tr>
<tr>
<td>Specificity</td>
<td>76.1 (71.7–80.1)</td>
<td>89.5 (86.1–92.2)</td>
</tr>
<tr>
<td>PPV</td>
<td>77.2 (73.0–81.0)</td>
<td>86.8 (82.6–90.2)</td>
</tr>
<tr>
<td>NPV</td>
<td>94.7 (91.5–96.7)</td>
<td>84.8 (81.1–88.0)</td>
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</table>
result was ductal carcinoma in situ. Fig. 3 shows ductal carcinoma in situ, diagnosed after repetition of pathology, as its TES was 5. Fig. 4 shows a sclerosing adenosis lesion with a TES of 3. Fig. 5 shows a case of encephaloid carcinoma with a TES of 4. Lastly, Fig. 6 illustrates an in situ ductal carcinoma with an invasive component that was interpreted on US as benign sclerosing adenosis lesion, yet with a TES of 4.

4. Discussion

Elasticity imaging is based on the premise that there is an inherent difference in the pliability of normal versus diseased tissue, and this difference can be measured as strain (displacement or elongation of tissue during manual compression) and displayed in real time during sonographic imaging (15). The first dynamic tests using real-time ultrasound to assess the compressibility of breast masses were introduced in the 1980s and have been used ever since (16). Over the years sonoelastography has evolved gradually from a relatively complicated method involving large and cumbersome hardware and complicated examination set-ups (18,19) to an elegant ultrasound-based technique. Real-time tissue elastography as it is available today is a dynamic method, which is mainly used for the evaluation of lesions in breast, prostate or thyroid tissue, axillary and mediastinal lymph nodes and for the assessment of force generation in skeletal muscle (17–19).

The sensitivity in our study for B-mode ultrasound, regarding all BI-RADS-US categories, was 95% and the specificity (76.1%) was rather poor, but this was increased up to 89.5%

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**Table 3** Comparison of pretest and posttest probability of disease (POD) within the subgroup of BI-RADS-US 3 lesions. 95% confidence interval in brackets.

<table>
<thead>
<tr>
<th>Tsukuba Elasticity Score 1–3 (test negative)</th>
<th>Tsukuba Elasticity Score 4–5 (test positive)</th>
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</thead>
<tbody>
<tr>
<td>Pretest POD</td>
<td>8.3 (4.9–13.6)</td>
</tr>
<tr>
<td>Posttest POD</td>
<td>3.1 (1.1–7.6)</td>
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<table>
<thead>
<tr>
<th>Tsukuba Elasticity Score 1–3 (test negative)</th>
<th>Tsukuba Elasticity Score 4–5 (test positive)</th>
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<tbody>
<tr>
<td>Pretest POD</td>
<td>56.6 (49.8–63.2)</td>
</tr>
<tr>
<td>Posttest POD</td>
<td>24.2 (16.3–34.3)</td>
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</tbody>
</table>

Table 4 Comparison of pretest and posttest probability of disease (POD) within the subgroup of BI-RADS-US 4 lesions. 95% confidence interval in brackets.

<table>
<thead>
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<th>Tsukuba Elasticity Score 1–3 (test negative)</th>
<th>Tsukuba Elasticity Score 4–5 (test positive)</th>
</tr>
</thead>
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<tr>
<td>Pretest POD</td>
<td>56.6 (49.8–63.2)</td>
</tr>
<tr>
<td>Posttest POD</td>
<td>24.2 (16.3–34.3)</td>
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</tr>
<tr>
<td>Posttest POD</td>
<td>24.2 (16.3–34.3)</td>
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</tbody>
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**Table 5** Comparison of sensitivity, specificity and positive (PPV) and negative predictive value (NPV) for sonoelastography with respect to the density of the breast. 95% confidence interval in brackets.

<table>
<thead>
<tr>
<th></th>
<th>ACR I–II</th>
<th>ACR III–IV</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>84.4 (77.8–89.4)</td>
<td>84.2 (76.6–89.7)</td>
</tr>
<tr>
<td>Specificity</td>
<td>82.7 (72.4–90.0)</td>
<td>92.81 (87.7–95.9)</td>
</tr>
<tr>
<td>PPV</td>
<td>91.0 (85.0–94.8)</td>
<td>89.6 (82.6–94.1)</td>
</tr>
<tr>
<td>NPV</td>
<td>72.0 (61.6–80.6)</td>
<td>88.82 (83.2–92.8)</td>
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</table>
by the use of realtime elastography. The results are comparable to those of Sadigh et al. (20) in a recent meta-analysis regarding all BI-RADS-US categories, where real time elastography demonstrated a sensitivity of 79% and an excellent specificity of 88% compared to conventional B-mode US (96% and 70%, respectively).

There are certain situations in which patients almost never receive a single imaging technique alone (i.e. conventional ultrasound, mammography or magnetic resonance imaging), but usually undergo several different examinations before receiving a final diagnosis. Therefore, in a realistic setting, sonoelastography is not applied as a single method but is used in addition to other examinations in “heavily pre-diagnosed patients” (21).

An elastogram, for example, might be capable of identifying a breast lesion as highly suggestive of malignancy, but if this lesion was already suspicious on the mammogram (i.e. BI-RADS 5) and/or in the conventional ultrasound (i.e. BI-RADS-US 5), this additional information would not have an effect on the management of the patient (21).

Therefore, we need to concentrate on patients and breast lesions where the appropriate action is as yet unclear and a more advanced assessment is needed. This is the rationale for our focus on patients with BI-RADS - US 3 and BI-RADS - US 4 lesions. Regarding BI-RADS - US 3 lesions the risk for malignancy is relatively low in this category, but can reach 3% or even more in distinct patient populations (22,13,23).

Our results demonstrate that the majority (91.7%) of BI-RADS-US 3 lesions are in fact benign. In those cases, which additionally showed a normal elastogram (Tsukuba Elasticity Score 1–3), the new negative predictive value was even higher by trend (96.9%). However, as soon as there was a suspicious elastogram, the risk for a malignant tumor increased significantly from 8.3% to a posttest probability of disease of 45.5%. Our results agreed with a recent study done by Wojcinski et al. (21) who were concerned with patients with
a sonographically visible lesion categorized as BI-RADS-US 3. They demonstrated that the pretest POD was 4.5% and rose significantly to 13.2% with a suspicious elastogram in the high-risk group.

If biopsy would be taken in these cases, we can estimate a maximal malignant/benign ratio of 1:3, which means that we can expect at least 1 carcinoma per 4 biopsies. Regarding the high posttest probability of disease, we encourage immediate histological verification of BI-RADS-US 3 lesions exhibiting a suspicious elastogram (Tsukuba Elasticity Score 4 or 5).

Lesions in BI-RADS US 4 category require histological verification. If there is no evidence of malignancy in specimen histology, no further steps are required. This approach implicates the risks that are associated with a false negative biopsy. The pretest probability of disease for BI-RADS-US 4 lesions in our study was 56.6%. Our results showed a significantly reduced posttest probability of disease of 24.2% for BI-RADS-US 4 lesions with a normal elastogram (Tsukuba Elasticity Score 1–3) and a significantly increased risk of 81.5% for lesions with a suspicious elastogram (Tsukuba Elasticity Score 4 or 5). Regarding the still high probability of disease after a normal elastogram, there should be no change in the clinical procedure in those cases. On the other hand, a suspicious elastogram indicates a highly increased risk for a malignant disease. Therefore, we suggest re-biopsy whenever there is a BI-RADS-US 4 lesion with a suspicious elastogram (Tsukuba Elasticity Score 4 or 5) but the specimen histology shows no malignancy since a false negative histological result is a possible scenario.

When comparing the results for sonoelastography with respect to the density of the breast, we found no difference regarding the identification of malignant lesions, but the negative predictive value and the specificity were higher in the ACR III–IV breasts than in ACR I–II breasts. This observation can be explained by the mechanical principles of sonoelastography: Real-time tissue elastography provides a relative measurement

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**Fig. 5** (A) B-mode US image and (B) USE image showed a hypoechoic circumscribed lesion exhibiting the features of a BI-RADS-US 3 lesion, displaying a mosaic pattern of green and blue but because the blue area is clearly larger the elasticity score was determined to be 4. Biopsy revealed encephaloid carcinoma.

**Fig. 6** (A) B-mode US image and (B) USE image revealed a small, hypoechoic rather ill defined lesion which was interpreted as sclerosing adenosis, with a Tsukuba Elasticity Score of 4. Pathology revealed in situ ductal carcinoma with invasive component.
of the elasticity of the tissue by comparing the different structures within the region of interest. So far, an absolute measurement is not available. Benign lesions usually present soft in sonoelastography. As the measurement of the lesion is only performed in relation to the surrounding tissue, even a benign lesion might appear relatively hard, if the adjacent tissue is relatively soft (24). Our results in this aspect agree with the model of an “elastographic contrast” that has been described by Wojcinski et al. (25) who stated that the “elastographic contrast” for benign lesions seems to be better in hard, which means dense, breast tissue. Consequently, the correct identification of benign lesions in a less dense breast seems to be more difficult with sonoelastography.

5. Conclusion

Our study demonstrates that there are no data that indicate a clinical advantage for the additional sonoelastographic evaluation of lesions that are categorized BI-RADS-US 0, 1, 2 or 5 in conventional ultrasound. However, for lesions that are categorized BI-RADS-US 3 or 4 in B-mode ultrasound our data provide evidence that an improved diagnostic performance can be achieved by adding real-time tissue elastography.

Conflict of interest

We have no conflict of interest to declare.

References