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● *Original Contribution*

# IMPLEMENTATION OF ELASTOGRAPHY SCORE AND STRAIN RATIO IN COMBINATION WITH B-MODE ULTRASOUND AVOIDS UNNECESSARY BIOPSIES OF BREAST LESIONS

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**Abstract—The aim of this study was to evaluate whether the combination of B-mode ultrasound, elastography score (ES) and strain ratio (SR) improves diagnostic performance with respect to breast lesions. One hundred thirty lesions were prospectively evaluated by B-mode ultrasound and strain elastography, followed by fine-needle aspiration cytology/biopsy in 117 woman who were scheduled for regular breast BUS. The median ES (4.5 vs. 2.9, $p < 0.001$) and SR (4.9 vs. 2.3, $p < 0.001$) were significantly higher for malignant than for benign lesions. A sensitivity of 90.5% and specificity of 93.2% for the ES (cutoff point = 3.8) and a sensitivity of 87.5% and specificity of 87.6% for the SR (cutoff point = 3.5) were obtained. Elastography combined with B-mode ultrasound improved the specificity, accuracy and positive predictive value. Receiver operating characteristic curves yielded a higher value for the combined technique for diagnosis of breast lesions. Routine use of such a diagnostic algorithm could reduce the number of unnecessary biopsies. (E-mail: Bojanic.kristina@gmail.com)     © 2016 The Authors. Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).**

*Key Words:* Breast lesions, Ultrasonography, Strain elastography, Elastography score, Strain ratio, Diagnostic accuracy, Breast Imaging Reporting and Data System.

## INTRODUCTION

Breast cancer is the most common cancer among women worldwide, with nearly 1.7 million cases diagnosed in 2012 (International Agency for Research on Cancer 2012). Breast cancer is also the most common cancer in women in Croatia, where it accounts for 26% of all cancer sites in females (Šamija and Strnad 2015).

Early detection of malignant lesions is critical for the successful management of breast cancer. Today, conventional B-mode ultrasound (BUS) plays a decisive role in the diagnostic pathways using the standardized Breast

Imaging Reporting and Data System (BI-RADS) lexicon developed by the American College of Radiology (ACR) (Mendelson et al. 2013). The distinct BI-RADS assessment category also implies which further clinical action should be taken.

Lesions graded as BI-RADS 3 are probably benign, and short-term follow-up is 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 (Sadigh et al. 2012a). On the other hand, a recent prospective study evaluating screening ultrasonography reported a BI-RADS 3 category in about 20% of patients, and 16.6% were ultimately sampled for biopsy with a low malignancy rate of 0.8% (Barr et al. 2013). BI-RADS 4 lesions have a

low to moderate probability of cancer (3%–94%) and biopsy/fine-needle aspiration cytology (FNAC) should be considered. However, with BI-RADS category 4, approximately 15% of findings are histologically malignant, and a much larger proportion of patients undergo invasive diagnostic procedures that might not be necessary if better imaging methods were available for accurate diagnosis confirmation (Liu et al. 2014). Presently, biopsy is used as a supplement for other diagnostic methods in the evaluation of breast lesions, but the rate of cancer detection in biopsies ranges from only 10% to 30% (Chiou et al. 2006; Duncan et al. 2000).

Fine-needle aspiration cytology is still widely practiced in the assessment of breast masses in both palpable and non-palpable lesions because it provides a rapid, accurate and cost-effective diagnosis in many countries, including Croatia (Radhakrishna et al. 2013). UK guidelines state a complete sensitivity >80%, positive predictive value of malignancy >95%, false-negative rate <5%, false-positive rate <1%, inadequacy rate of 3 <25% and suspicious rate <20%, confirming that FNAC as a very good and effective diagnostic modality (Wells et al. 1994).

According to Medina-Franco et al. (2005) and Abdullateef (2014), FNAC in the hands of an experienced examiner achieves very high sensitivity and specificity and low false-positive and false-negative rates and is associated with no significant complications. They concluded that the diagnostic accuracy of FNAC for breast lesions is very high with minimal complications. A positive predictive value of 100% allows establishment of a therapy based on its results. Furthermore, the Croatian health care system is financially limited, and FNAC is the method of choice for diagnosis of invasive breast lesions. Therefore, a suitable predictor of malignancy in BI-RADS 3 and 4 lesions would be beneficial and of great clinical relevance. To improve diagnostic accuracy, strain elastography (SE) was introduced (Ophir et al. 1991). It is a non-invasive technique in which stiffness or strain images are used to detect or classify anatomic areas with different elasticity patterns. This technique, based on tissue stiffness/elasticity, helps in the differential diagnosis of benign and malignant breast lesions (Moon et al. 2011) that conventional ultrasound methods cannot detect, thus improving the accuracy of diagnosis of breast cancer (Pons et al. 2015) and reducing the number of unnecessary biopsies of BI-RADS 3 and 4 lesions.

According to the European Federation for Ultrasound in Medicine and Biology (EFSUMB) guidelines and recommendations on the clinical use of ultrasound elastography from 2013, elastography was initially recommended to increase diagnostic confidence in determination of benign or malignant lesions, as well as to re-grade benign-appearing stiff lesions and consider them for biopsy, but not to downgrade a lesion that would be sent for biopsy on the basis of ultrasound descriptors alone (BI-RADS 4A or higher) (Cosgrove et al. 2013).

Recent studies and a meta-analysis (Sadigh et al. 2012a, 2012b, 2013) indicated that ultrasound elastography provides higher image quality compared with BUS or mammography during breast cancer diagnosis, which can increase specificity and reduce false-positive results, making it useful for avoiding breast biopsy (Barr 2014; Faruk et al. 2015; Sadigh et al. 2012a). Strain elastography allows evaluation of the elastography score (ES) as a qualitative parameter of relative stiffness of the lesion (Barr 2012) and the strain ratio (SR, fat/lesion ratio [FLR]) as a semiquantitative ratio of the stiffness of the lesion to that of fat (Barr 2012; Yoon et al. 2014). According to the World Federation for Ultrasound in Medicine and Biology (WFUMB) guidelines and recommendations for clinical use of ultrasound elastography, SR is a semiquantitative method for numerically evaluating how many times stiffer a target mass is compared with subcutaneous fat (Barr et al. 2015). Although some studies have reported that the SR is a highly valuable and more objective parameter for differentiating malignant and benign breast lesions than the ES (Shyam et al. 2012; Thomas et al. 2010; Yoon et al. 2014), others have confirmed that the SR has poor reliability and does not improve elastographic accuracy (Kumm and Szabunio 2010; Yerli et al. 2011). Additionally, only a few studies have investigated the usefulness and accuracy of SE with different-sized breast lesions (Giuseppetti et al. 2005; Itoh et al. 2006; Liu et al. 2014).

Therefore, a prospective study was designed to evaluate whether the combination of conventional B-mode ultrasound, ES and RS improves diagnostic performance and increases confidence during examination of women with breast lesions in everyday clinical practice. We also wanted to examine the influence of lesion size on the degree of elasticity. Additionally, we aimed to determine whether ES and SR, as strong predictors of malignant and benign changes, could downgrade BI-RADS 3 and 4 lesions and reduce the rate of unnecessary invasive diagnostic procedures.

## METHODS

### Patients

The study was reviewed and approved by the Health Center Osijek Review Board (Approval No. 03-382/14). All participants signed an informed consent form before being included in the study. One hundred seventeen women scheduled for regular breast ultrasound examination from January 2014 to May 2015 at the Department of Ultrasound Diagnostics at the Health Center Osijek were included in the study. To be included the women had to

have a new hypo-echoic or iso-echoic focal breast lesion suspected of being a solid mass (compared with subcutaneous fatty tissue) classified as BI-RADS 2–5. Regardless of the ultrasonographic findings, each lesion in the study was subjected to a cytological/histologic examination with the consent of the patient. Eight lesions categorized as BI-RADS 2 in our study underwent FNAC at the request and insistence of the patients.

Excluded from the study were (i) anechoic lesions (clearly cystic), (ii) lesions with inconclusive/no available cytologic/histopathologic diagnosis, (iii) lesions larger than 30 mm in diameter, and (iv) lesions positioned close to the skin or the rib cage. According to the 2013 EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography, lesions positioned close to the skin or rib cage and lesions larger than the ultrasound field of view could yield poor-quality elastograms and unreliable results (Cosgrove et al. 2013).

*Elastography and analysis*

One of four radiologists with 5 to 7 y of experience in the performance of breast ultrasound and with knowledge of the clinical and mammographic findings performed conventional BUS and real-time SE on 130 focal breast lesions using a Logiq Expert 7 ultrasound scanner (General Electric, Fairfield, CT, USA) with 11 L-D (5–13 MHz) and 9 L-D (3–8 MHz) linear array transducers. Mainly the 11 L-D linear array transducer was used because of its better resolution. The 9 L-D (3–8 MHz) probe has better penetration and was used only in voluminous breasts with more deeply located lesions. The four operators had accrued 4 to 6 mo of experience with ultrasound elastography before this study. First, bilateral whole-breast conventional BUS was performed while patients were in the supine position with their arms placed behind their head. The breast tissue was examined systematically using a radial scanning pattern. B-Mode pictures of the lesions were documented in two planes. Each lesion was assigned a BI-RADS category using the ACR BI-RADS lexicon of ultrasonographic descriptors of lesion echo pattern, shape, orientation, margin and posterior acoustic features. The lesions were divided into three groups based on their size (group I, <1 cm; group II, between 1 and 2 cm; group III, between 2 and 3 cm) to explore the usefulness of SE with different-sized breast lesions. Next, SE was performed and, as previously reported, the orientation of the probe did not influence the elastographic score (Ciurea et al. 2011). Therefore, elastograms were taken in either the sagittal or horizontal orientation. For data acquisition, a field-of-view box was set to include the region from the subcutaneous fat layer to the superficial portion of the pectoralis muscle layer, and transverse and longitudinal real-time imaging of the breast lesion was performed.

The target lesion was vertically compressed as the operator applied very light pressure to the transducer. Operators avoided using high levels of pressure, which manifests as non-linear properties of tissue elasticity; in such circumstances, the association between pressure and strain is no longer proportional, and false results may be obtained. During the exam, an adequate probe pressure on the target lesion was displayed in *green* in the vertical column on the monitor of the ultrasound scanner; a partially adequate pressure was displayed as *yellow* and an inadequate as *red*. This helped the operator to record the best elastography results. According to the 2013 EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography, a sequence stored in the cine loop should be reviewed and the most reproducible frame selected for elastography analysis (Cosgrove et al. 2013). Consequently all elastography studies were saved as video files for subsequent analysis by three radiologists who independently analyzed results until a consensus was reached. The ES and SR were measured on a representative static image, including the coupled B-mode and elastography images. Inside the field-of-view box, we positioned the first region of interest (ROI) in lateral subcutaneous fat tissue at the same depth as the target lesion, and with the second ROI, we outlined the entire target lesion. The ES was interpreted according to the 5-point Tsukuba classification proposed by Itoh et al. (2006); a score of 1 indicates even strain for the entire hypo-echoic lesion (*i.e.,* the entire lesion was evenly shaded in *green*) (Fig. 1). A score of 2 indicates strain in most of the hypo-echoic lesion, with some areas of no strain (*i.e.,* the hypo-echoic lesion has a mosaic pattern of *green* and *blue*) (Fig. 2). A score of 3 indicates strain at the periphery of the hypo-echoic lesion, with sparing of the center of the lesion (*i.e.,* the peripheral part of the lesion was *green*, and the central part was *blue*) (Fig. 3). A score of 4 indicates no strain in the entire hypo-echoic lesion (*i.e.,* the entire lesion was *blue*, but its surrounding area was not included) (Fig. 4). Finally, a score of 5 indicates no strain in the entire hypo-echoic lesion or in the surrounding area (*i.e.,* both the entire hypo-echoic lesion and its surrounding area were *blue*) (Fig. 5). Lesions categorized as ES 1, 2 or 3 were considered probably benign, and lesions categorized as ES 4 and 5 were suspicious for cancer (Gheonea et al. 2011; Goddi et al. 2012; Wojcinski et al. 2013). In addition to the most frequently used Tsukuba scoring system proposed by Itoh et al. (2006), a multicentric Italian study proposed a different classification system that takes both solid and cystic lesions into account (Rizzatto 2007). They additionally described the new three-layered score (as score 1), observed in cystic lesions, but we have not used it because anechoic, clearly cystic lesions were excluded from our study. Calculation of the SR was based on a
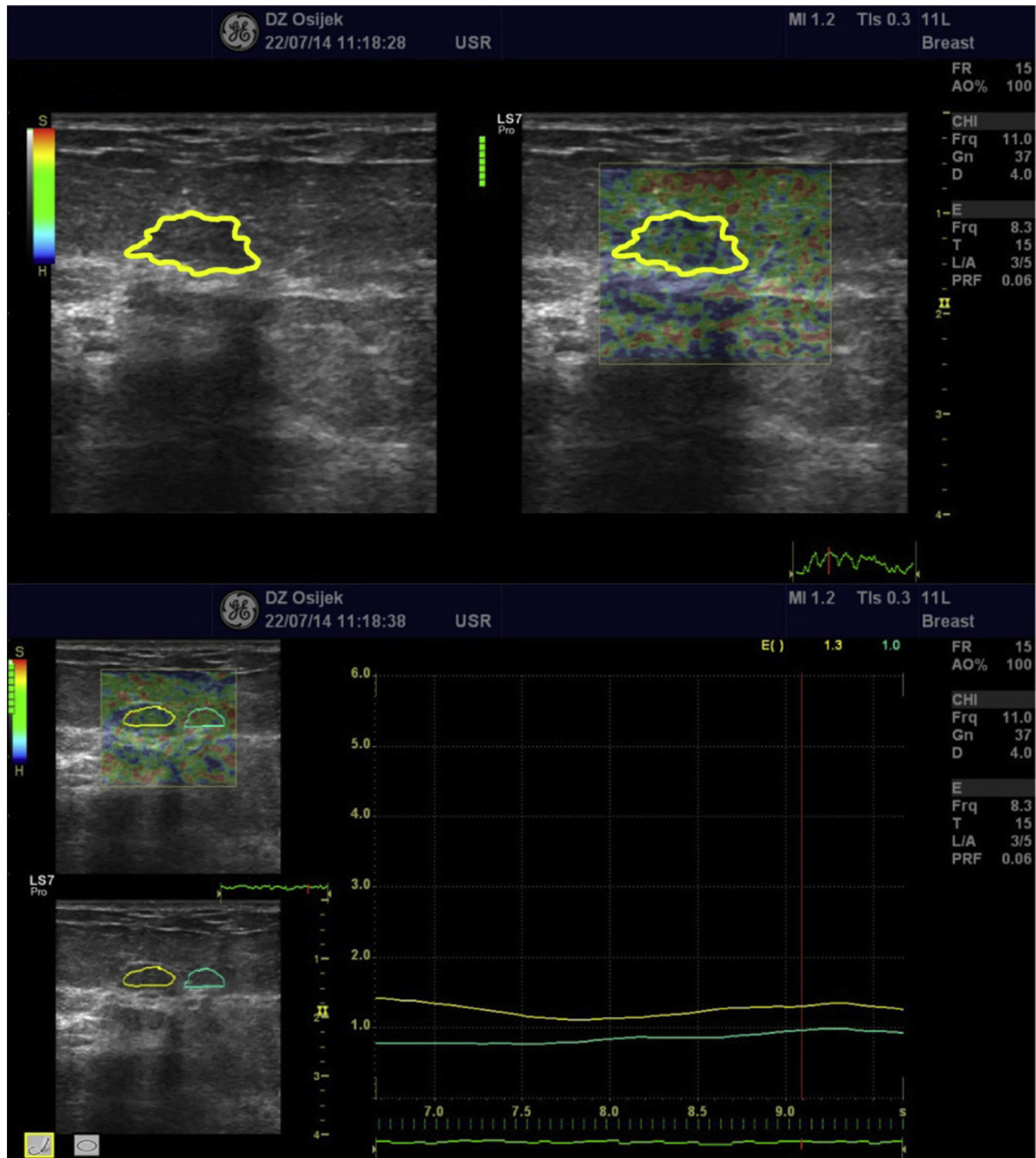
Fig. 1. Newly diagnosed solid mass in 1-y interval with low suspicion for malignancy in a 47-y-old woman. Top left: On the basis of a conventional B-mode image, the lesion was classified as BI-RADS 3. Top right: On elastographic imaging, the entire lesion was evenly shaded *green*, as was the surrounding breast tissue. Bottom: Additional quantitative analysis of the same lesion yielded an elasticity score of 1.3. Fine-needle aspiration cytology revealed a lipoma.

comparison of the average strains measured in the lesion and adjacent fatty tissue at the same depth (Barr 2012; Barr et al. 2015; Yoon et al. 2014).

By use of ROC analysis, optimal cutoff values for ES and SR were determined, and a modified BI-RADS category was calculated according to the following equation: Modified BI-RADS = BI-RADS + $\alpha$ + $\beta$, where $\alpha$ and $\beta$ are the ES and SR scores, respectively (Lee et al. 2014; Liu et al. 2014; Yoon et al. 2014). When the ES value was higher than the cutoff point, $\alpha$ was scored as +1; when the ES value was lower than the cutoff point, $\alpha$ was scored as −1; when it was equal
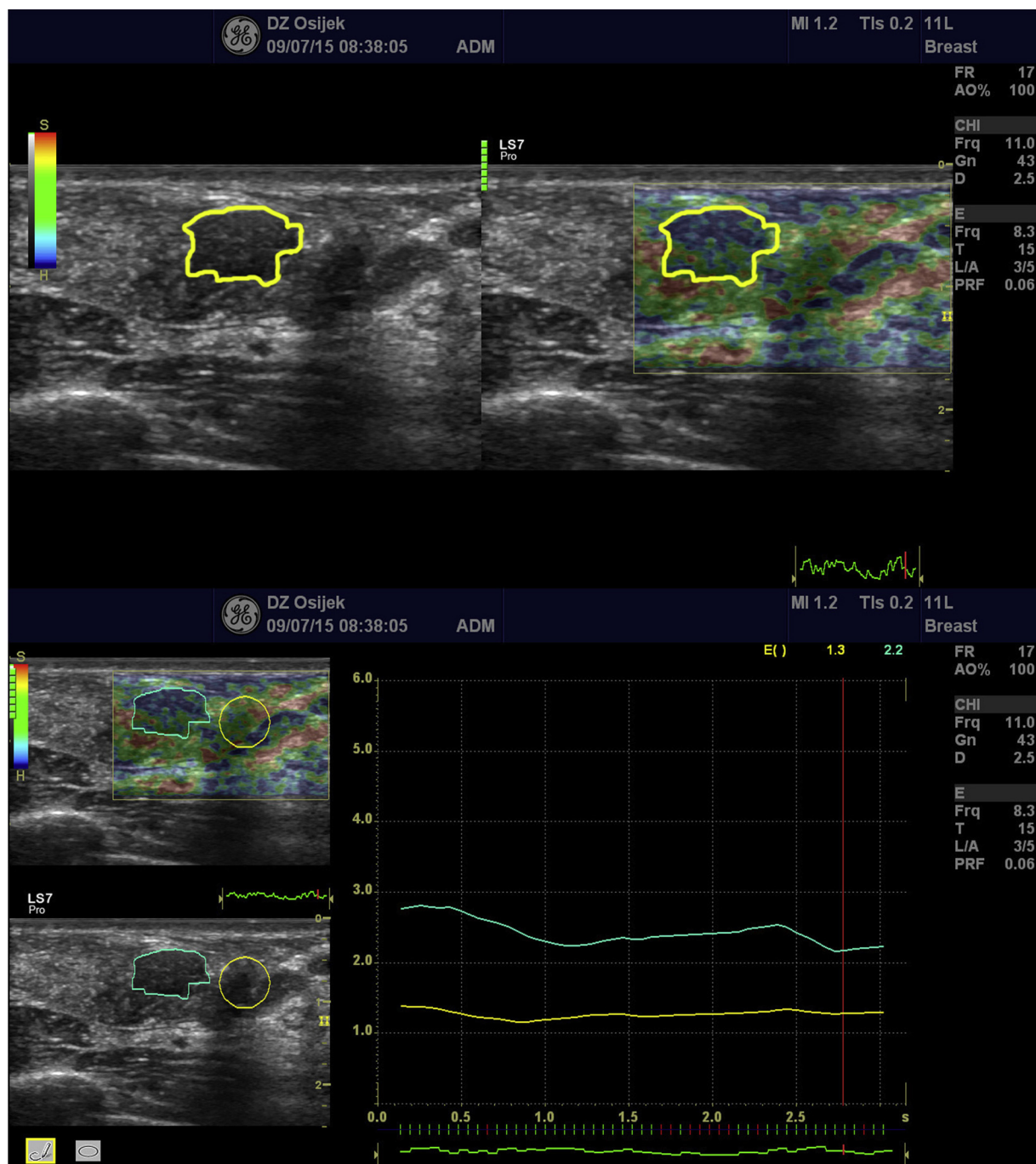
Fig. 2. Newly diagnosed solid mass in 1-y interval with low suspicion for malignancy in a 46-y-old woman with a positive family history of breast cancer. Top left: On the basis of a conventional B-mode image, the lesion was classified as BI-RADS 3. Top right: On elastographic imaging, the entire lesion manifested a mosaic pattern of *green and blue*. Bottom: Additional quantitative analysis of the same lesion yielded an elasticity score of 2.1. Fine-needle aspiration cytology revealed a fibroadenoma.

to the cutoff point, we estimated the $\alpha$ score as 0. When the SR value was higher than the cutoff point, $\beta$ was scored as $+1$; when the SR value was lower than the cutoff point, $\beta$ was scored as $-1$; when it was equal to the cutoff point, we estimated the $\beta$ score as 0. When

the modified BI-RADS score was calculated as $<2$, the score was recorded as 2; scores higher than 5 were recorded as 5.

The cytologic/histopathologic results obtained from ultrasound guided FNAC/core biopsy or operation
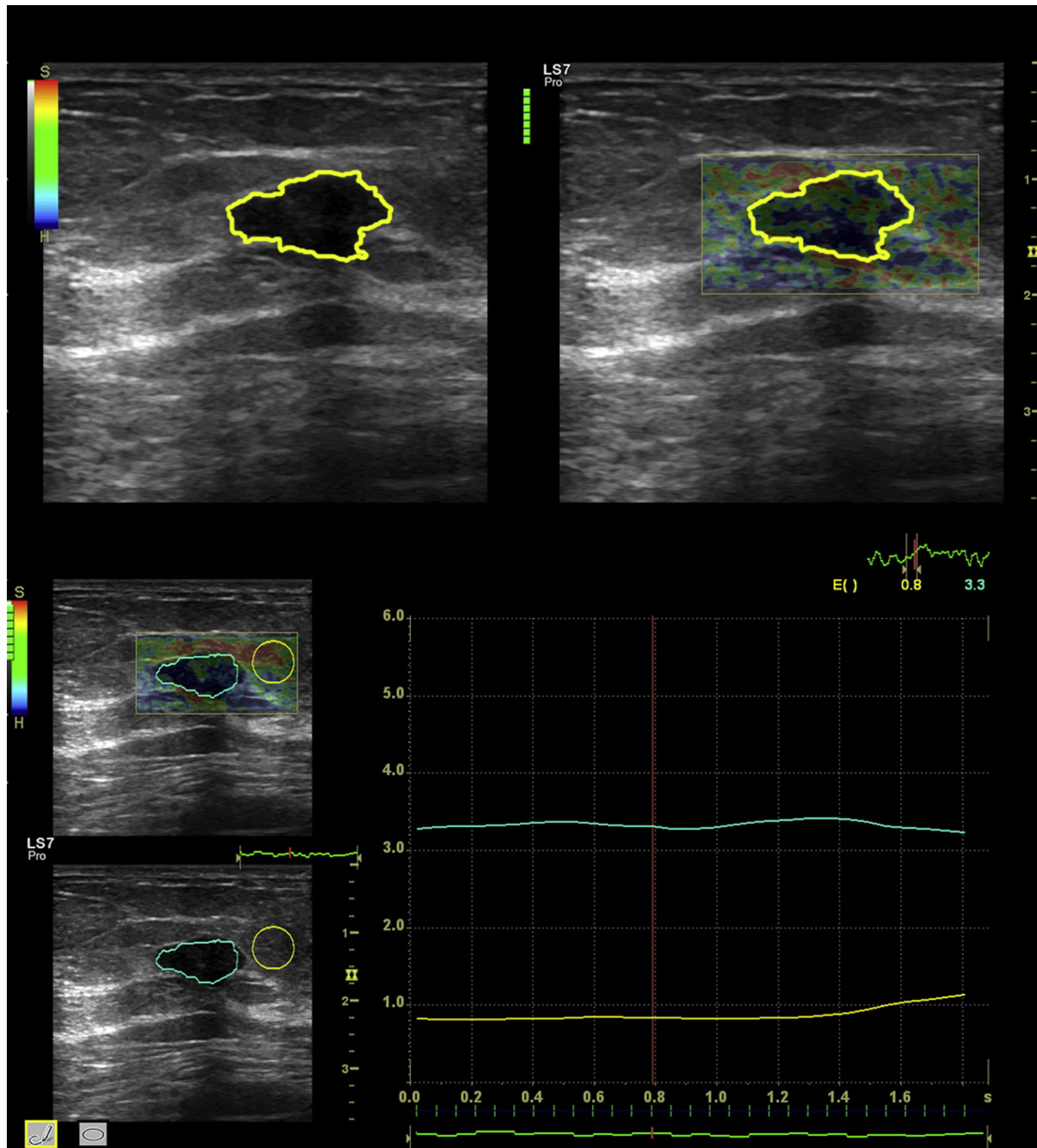
Fig. 3. Newly diagnosed solid mass with intermediate suspicion for malignancy in a 68-y-old woman. Top left: On the basis of a conventional B-mode image, the lesion was classified as BI-RADS 4. Top right: On elastographic imaging, the lesion was mostly *blue* with some *green* parts. Bottom: Additional quantitative analysis of the same lesion yielded an elasticity score of 3.3. Fine-needle aspiration cytology revealed a fibroadenoma.

excisions were used as the reference standard. All lesions underwent FNAC as the first step and all malignant FNAC lesions (42) underwent core needle or open biopsy. Out of 88 benign lesions 13 had FNAC category C3 (atypical, probably benign) and underwent core biopsy as well.

*Statistical analysis*

Data were described using descriptive statistical methods. The Mann–Whitney $U$ test and Kruskal–Wallis test were used to compare the median between two groups, while the $\chi^2$ test and Fisher's exact test were used to analyse the differences between proportions.
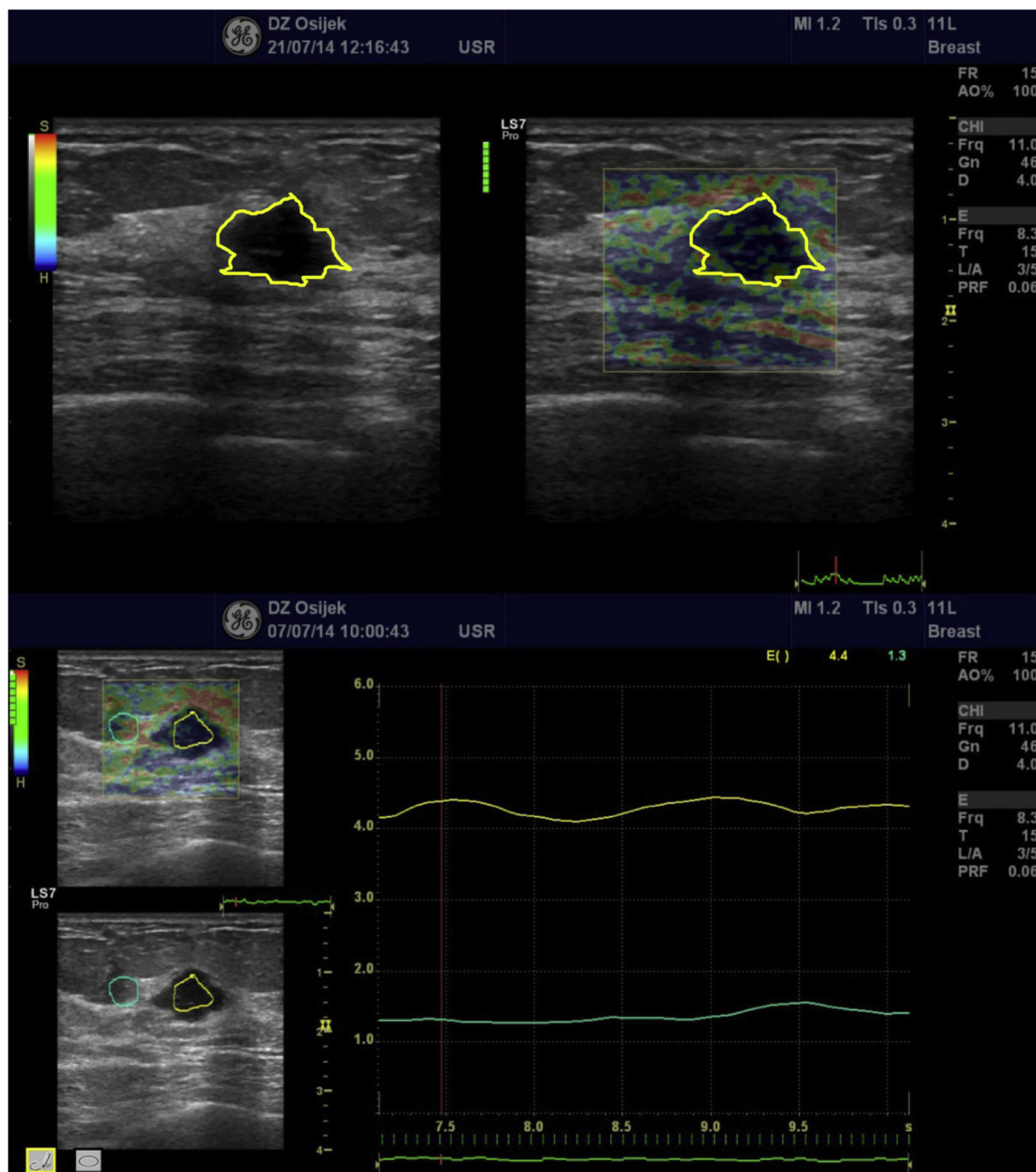
Fig. 4. Newly diagnosed suspicious solid mass in 1-y interval in a 54-y-old woman. Top left: On the basis of a conventional B-mode image, the lesion was classified as BI-RADS 4B. Top right: On elastographic imaging, the entire lesion was evenly shaded *blue*. Bottom: Additional quantitative analysis of the same lesion yielded an elasticity score of 4.4. Core biopsy revealed invasive ductal carcinoma.

Receiver operating curve (ROC) analysis was used to determine the optimal threshold, area under the curve (AUC), specificity and sensitivity of the tested parameters. Spearman's rho test was used to determine the association between non-normally distributed variables.

The level of significance was set at a $p$ value of 0.05. Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA), while the ROC analysis used MedCalc 11.5.0 (MedCalc Software, Ostend, Belgium).
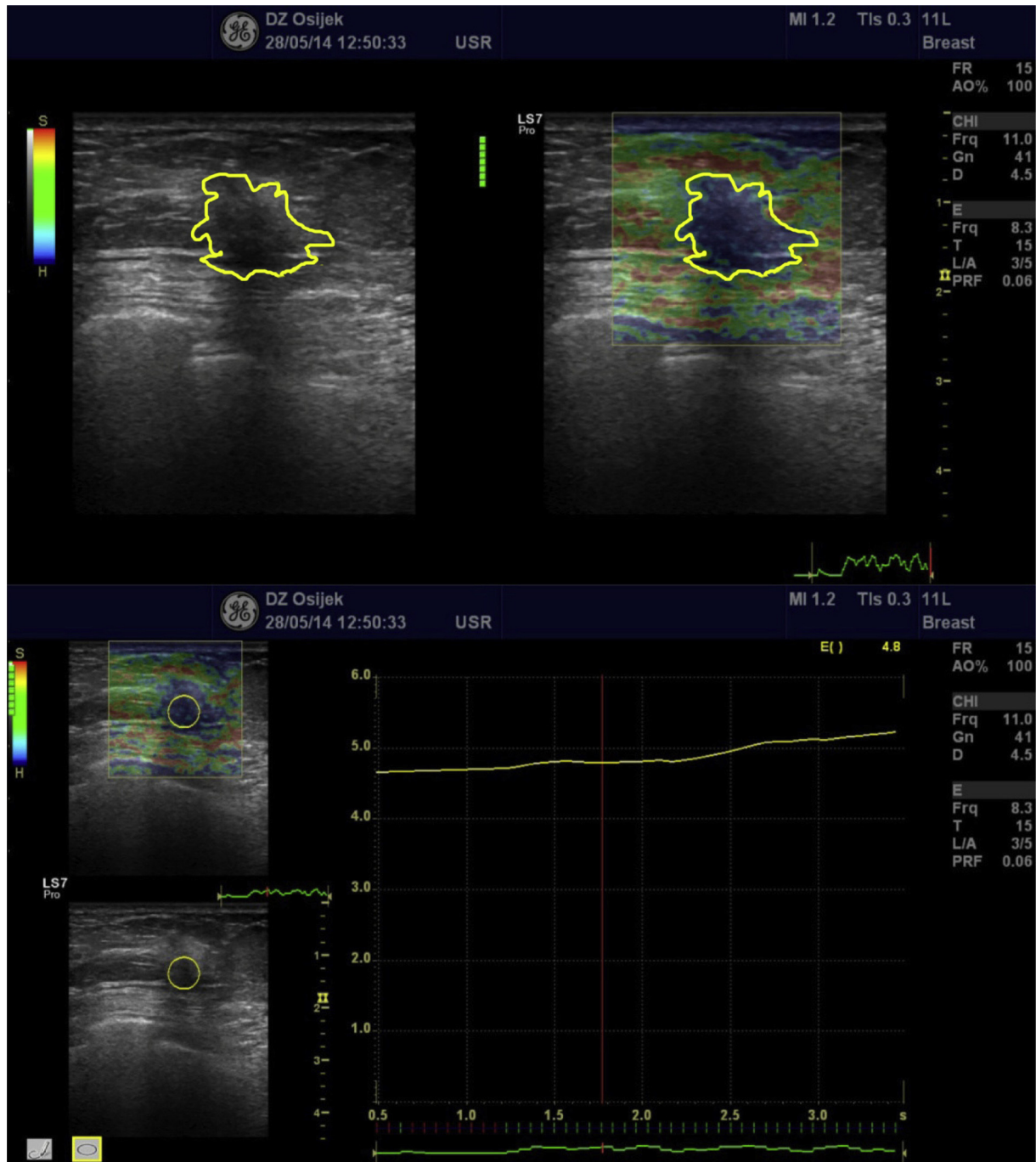
Fig. 5. Newly diagnosed highly suspicious solid mass in a 68-y-old woman. Top left: On the basis of a conventional B-mode image, the lesion was classified as BI-RADS 5. Top right: On elastographic imaging, both the entire lesion and its surrounding area were shaded *blue*. Bottom: Additional quantitative analysis of the same lesion yielded an elasticity score of 4.8. Surgical excision revealed a highly invasive, not otherwise specified carcinoma.

## RESULTS

We included 117 women with 130 hypoechoic and isoechoic focal breast lesions (mean age for benign lesions 50 y and 63 y for malignant lesions; age range 27–82). There were 88 (68%) benign and 42 (32%) malignant lesions. All 88 benign lesions were solid and among them the most common lesions were fibroadenoma (43%) and fibrocystic changes (23%). Among malignant nodules, the most common lesion was infiltrative ductal carcinoma (69%). Patients with malignant

Table 1. Mean values of variables with respect to cytologic/histopathologic results

| Researched variables | Median (interquartile range) | | | $p^*$ |
| | Benign | Malignant | Total | |
| --- | --- | --- | --- | --- |
| Age | 50 (42–58) | 63 (55–69) | 54 (44–63) | <0.001 |
| BI-RADS category | 2 (2–3) | 3 (3–5) | — | <0.001 |
| BI-RADS category + elastography | 2 (2–3) | 5 (4–6) | — | <0.001 |
| Strain ratio | 2.3 (1.5–3.1) | 4.9 (3.8–6.1) | | <0.001 |
| Elastography score | 2.9 (2.1–3.3) | 4.5 (4.2–4.5) | | <0.001 |

\* Mann Whitney test.

lesions were significantly older (Mann–Whitney test, $p < 0.001$), had a higher ES and SR (Mann–Whitney test, $p < 0.001$), a higher BI-RADS category (Mann–Whitney test, $p < 0.001$) and a higher modified BI-RADS category (Mann–Whitney test, $p < 0.001$) compared to patients with benign lesions, as shown in Table 1. The median ES for benign lesions was 2.9, with an interquartile range of 2.1–3.3. Breast carcinoma showed a median ES of 4.5 (4.2–4.5). The median SR for malignant lesions was 4.9 (3.8–6.1), which was significantly higher than that for benign lesions, which had a median of 2.3 (1.5–3.1). ROC analysis showed that the area under the curve was 0.834 for conventional ultrasound, 0.954 for ES and 0.920 for SR. ROC curves have not shown a significant difference between ES and SR (differences between areas = 0.0341, 95% confidence interval from 0.0292 to 0.0974, $p = 0.291$) in the diagnosis of breast lesions (Fig. 6). Using receiver operating characteristic (ROC) analysis, we found that 3.8 is the optimal cutoff value for the ES, with a sensitivity of 90.5%, specificity of 93%, positive predictive value (PPV) of 86%, negative predictive value (NPV) of 95% and accuracy of 92.3%. Also we determined that the optimal cutoff value for the SR was 3.5, with a sensitivity of 87.5%, specificity of 87.6%, PPV of 75.5%, NPV of 93.8% and accuracy of 86.9%.

The sensitivity, specificity and accuracy for the combined use of BUS and SE were 97.6%, 88.6% and 91.5%, respectively, and the area under the curve was 0.913. ROC curves yielded higher values for the combined BUS and SE technique in the diagnosis of breast lesions ($p < 0.05$) (Fig. 7).

Of 70 lesions classified as BI-RADS 4 by conventional ultrasound descriptors, 29 were found to be malignant and 41 benign. Among these 70 BI-RADS 4 breast lesions, 31 were characterized as benign owing to their elasticity, and the diagnosis of benignity was correctly predicted in 76% of cases. Conventional ultrasound had a sensitivity, specificity and accuracy of 41.4%, 21.7% and 32.3%, respectively, whereas the diagnostic sensitivity, specificity and accuracy of SE were 55.7%, 80% and 66.9%, respectively.

The distribution of lesions according to size and cytologic findings is outlined in Table 2. Mean elastography parameters with respect to lesion size on conventional ultrasound images are listed in Table 3. The mean value for each lesion size category was significantly higher for malignant lesions than for benign lesions (Mann–Whitney $U$-test, $p < 0.001$). ES or SR values according to lesion size did not significantly differ within each group size. When the diagnosis obtained with the combined technique (conventional ultrasound + strain elastography) with the results obtained from the cytologic workup, correct prediction of findings was most common for lesions 2–3 cm in size (Cohen's $\kappa = 0.901$), as outlined in Table 4, with a sensitivity of 100%, specificity of 92.3%, PPV of 88.9%, NPV of 100% and accuracy of 95.2%.
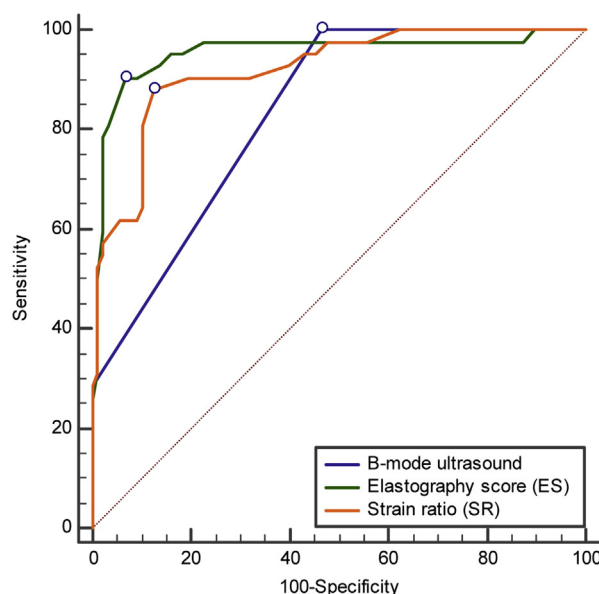


Fig. 6. Receiver operating characteristic (ROC) curves for B-mode ultrasound (BUS), elasticity score (ES) and strain ratio (SR). The areas under the ROC curves differed significantly between BUS and ES (difference between areas = 0.120, 95% confidence interval [CI]: 0.0578–0.183, $p < 0.001$) and between BUS and SR (difference between areas = 0.0862, 95% CI: 0.0199–0.152, $p = 0.011$); however, ROC curves do not reveal a significant difference between the ES and SR (difference between areas = 0.0341, 95% CI: 0.0292–0.0974, $p = 0.291$).
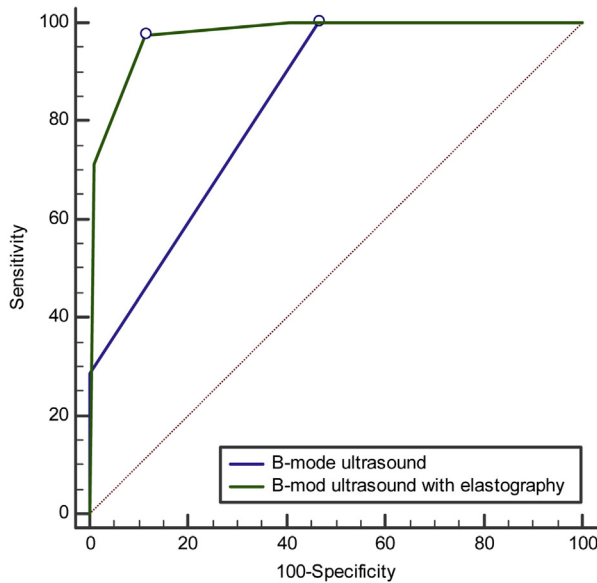
Fig. 7. Receiver operating characteristic (ROC) curves for B-mode ultrasound (BUS) and combined technique. The areas under the ROC curves differed significantly between BUS and the combined technique (difference between areas = 0.140, 95% confidence interval: −0.0896 to 0.190, $p < 0.001$).

## DISCUSSION

Elastography score and strain ratio are the two types of elastography interpretation parameters analyzed in our study. Additionally, we used cutoff values for the ES and SR to modify the BI-RADS category and determine further diagnostic actions, especially for BI-RADS 4 lesions. Our results for the ES are in accordance with other recent studies (Gheonea et al. 2011; Itoh et al. 2006; Liu et al. 2014; Menezes et al. 2016). ROC analysis revealed that ES performed better diagnostically than conventional ultrasound or SR. Furthermore, in our study, the combination of ES and BUS had better specificity and accuracy than the combination of SR and BUS in distinguishing benign from malignant breast lesions, which is in concordance with the review by Carlsen et al. (2013). They presented an overview of strain elastography and its applications in breast cancer diagnostics and analyzed eight studies. Three of the eight studies additionally evaluated the diagnostic performance of ES

Table 2. Distribution of lesions by size with respect to cytologic/histopathologic results

| Size | No. (%) of lesions | | | $p^*$ |
|------|--------|-----------|-------|-----|
| | Benign | Malignant | Total | |
| >1 cm | 40 (45.5) | 17 (40.5) | 57 (43.8) | 0.784 |
| 1–2 cm | 35 (39.8) | 17 (40.5) | 52 (40) | |
| 2–3 cm | 13 (14.8) | 8 (19) | 21 (16.2) | |
| Total | 88 (100) | 42 (100) | 130 (100) | |

* Fisher exact test.

with that of SR. All three studies reported a decrease in specificity when using SR instead of ES. Overall accuracy decreased in two of the three studies. Sensitivity decreased in all eight studies comparing BUS with ES, and specificity and accuracy increased in seven of eight studies, which is in accordance with our results. Better agreement (Cohen's $\kappa = 0.812$) with cytologic/histologic findings was obtained with the ES, which recognized 38 of 42 lesions (90.5%) as malignant. The ES was more efficient in representing tissue stiffness, although it measures only the relative stiffness of the lesion.

The SR, as a semiquantitative measurement, should yield more objective results. Several studies have found that this parameter can objectively quantify strain within a lesion compared with surrounding fatty tissue and determine whether a lesion is benign or malignant using cutoff points of 2.45 (Thomas et al. 2010), 3.65 (Gheonea et al. 2011), 4.15 (Liu et al. 2014), 4.8 (Barr 2012) and 5.6 (Alhabshi et al. 2013). The differences in the cutoff values among these studies can be partly explained as a result of pre-compression, especially when the diagnosis has been established by a radiologist with inadequate clinical experience. Pre-compression can substantially change the strain value of fat. As pre-compression is applied, the stiffness of all tissues increases. However, the stiffness variations in fat tissue are more prominent than those in normal breast tissue and masses; therefore, with pre-compression, the SR will decrease. The other reason that could explain the SR results obtained in our and other studies is ROI inconsistency. The ROI for fat measurement should contain only fat, and measurements should be taken at the same depth in the image, as the degree of compression varies with depth. However, this is not always possible in clinical practice. Apart from pre-compression and ROI selection inconsistency, strain elastography as an imaging modality requires external compression. Because external compression is applied manually, strain elastography is operator dependent, which influences its reproducibility. Yerli et al. (2011) determined if the combination of ES and SR was useful in distinguishing benign from malignant lesions. They concluded that after evaluation of lesions with the Tsukuba elasticity scoring system, additional evaluation of the SR increased calculation time and did not contribute to the differentiation between benign and malignant lesions. Menezes et al. (2016) assessed four elastography criteria (elastography score, strain ratio, distance ratio and area ratio) and reported that all four were able to differentiate benign and malignant lesions, but the ES was the most accurate. This is in agreement with our results that either ES or SR was able to differentiate benign and malignant lesions with statistical significance. Kumm and Szabunio (2010) reported lower sensitivity, specificity, and negative and

Table 3. Values of elasticity parameters by lesion size, with cytologic results as reference standard

| Elasticity parameters | Median (interquartile range) | | | | $p*$ |
| | <1 cm | 1–2 cm | 2–3 cm | Total | |
| --- | --- | --- | --- | --- | --- |
| Elastography score | | | | | |
|   Benign | 2.9 (2.1–3.4) | 3.0 (2.4–3.3) | 2.1 (1.6–3.0) | 2.9 (2.1–3.3) | 0.169 |
|   Malignant | 4.5 (4.0–5.0) | 4.5 (4.2–4.9) | 4.4 (4.3–4.8) | 4.5 (4.2–5.0) | 0.775 |
|   $p*$ (between benign and malignant groups by lesion size) | <0.001 | <0.001 | <0.001 | <0.001 | |
| Strain ratio | | | | | |
|   Benign | 2.1 (1.5–3.1) | 2.75 (1.9–3.0) | 2.0 (1.35–3.4) | 2.3 (1.5–3.1) | 0.441 |
|   Malignant | 5.6 (3.9–6.9) | 4.1 (3.7–5.2) | 5.4 (4.2–5.9) | 4.9 (3.8–6.1) | 0.124 |
|   $p*$ | <0.001 | <0.001 | <0.001 | <0.001 | |

* Kruskal Wallis test for $p$ in horizontal column and Mann Whitney U test for $p$ in vertical column.

positive predictive values for ES and SR compared with previously published results, and they concluded that the clinical value of elastography should depend on its ability to minimize false-negative results. Ideally, the NPV would approach 0.98. This value was achieved in our study when we combined BUS with ES and SR (NPV of combined technique was 98.7%). According to the ROC analysis in our study, the best diagnostic performance was achieved when BUS was combined with both ES and SR (Cohen's $\kappa = 0.826$), with the area under the curve of 0.973, which is in agreement with some studies (Liu et al. 2014; Thomas et al. 2010). According to the results we obtained, combined use of BUS and SE would have reduced the biopsy rate for BI-RADS 4 lesions (31/70). We found that, of 41 benign lesions, the elasticity of 31 lesions indicated benignity. The diagnosis of benignity was correctly predicted in 76% of cases with the combined use of BUS, ES and SR, suggesting that these patients underwent unnecessary biopsy procedures.

This study also examined the usefulness of elastography for diagnosis of patients with different-sized breast lesions. Recent results of similar studies are inconsistent.

Table 4. Distribution of lesions by lesion size and results of combined technique, with cytologic findings as reference standard

| Combined technique | No. (%) of lesions | | Total | $p*$ | Cohenov $\kappa$ |
| | Benign | Malignant | | | |
| --- | --- | --- | --- | --- | --- |
| Lesions <1 cm | | | | | |
|   Benign | 35 (87.5) | 1 (5.9) | 36 (63.2) | <0.001 | 0.764 |
|   Malignant | 5 (12.5) | 16 (94.1) | 21 (36.8) | | |
|   Total | 40 (100) | 17 (100) | 57 (100) | | |
| Lesions 1–2 cm | | | | | |
|   Benign | 31 (88.6) | 0 | 31 (59.6) | <0.001 | 0.835 |
|   Malignant | 4 (11.4) | 17 (100) | 21 (40.4) | | |
|   Total | 35 (100) | 17 (100) | 52 (100) | | |
| Lesions 2–3 cm | | | | | |
|   Benign | 12 (92.3) | 0 | 12 (57.1) | <0.001 | 0.901 |
|   Malignant | 1 (7.7) | 8 (100) | 9 (42.9) | | |
|   Total | 13 (100) | 8 (100) | 21 (100) | | |

* Fisher exact test.

Giuseppetti et al. (2005) reported sensitivities of 86% and 65% and specificities of 100% and 62% for lesions <2 cm and >2 cm in diameter. They emphasized that lesion size influenced the degree of elasticity. Itoh et al. (2006) reported that within each size category, the difference between ES values for malignant and benign lesions was significant and did not depend on lesion size for lesions <30 mm in diameter. Liu et al. (2014) reported that elastography provides more information for diagnosing small breast lesions, as reflected by higher specificity and accuracy values in group II (between 1 and 2 cm) compared with other groups. They concluded that most small malignant lesions do not contain necrotic tissue as the internal component, and the hardness of the lesions is relatively homogeneous. For large lesions, calcification, fibrosis and necrosis may be present within the lesion, resulting in uneven hardness possibly false-negative results. Interestingly, in our study, size-correlated analysis provided higher specificity and accuracy in group III (lesions between 2 and 3 cm) compared with other groups, as outlined in Table 5. However, this topic is yet to be investigated more thoroughly and may be the subject of further studies.

Our study had several limitations. The most prominent one is that the acquisition of elastograms, as well as analysis, was observer dependent. The magnitude of initial compression could affect the elasticity map. Furthermore, the study was based on fixed B-mode images instead of video clips, which makes it even more observer dependent. BI-RADS 4 lesions were not divided into subgroups 4A, 4B and 4C, which could affect the accuracy of our results. Therefore, precise analysis of a larger number of BI-RADS 4 lesions is recommended. All lesions underwent FNAC as the first step, and afterward, only FNAC category C3 (atypical, probably benign; 13 lesions) and malignant FNAC lesions (42 lesions) underwent core biopsy or surgical excision.

In addition, inter-observer or intra-observer variability in performing and interpreting elastography was not analyzed. One might point to this shortcoming as a

Table 5. Sensitivity, specificity, PPV, NPV and accuracy of diagnostic procedures by lesion size compared with fine-needle aspiration cytology/core biopsy findings*

| Comparasion with FNAC/biopsy findings | Sensitivity, % | Specificity, % | PPV, % | NPV, % | Accuracy |
|---|---|---|---|---|---|
| <1 cm | 94.11 (69.3–99.7)* | 87.5 (72.3–95.3) | 76.2 (52.5–90.9) | 97.2 (83.8–99.8) | 89.47 |
| 1–2 cm | 100 (77.1–100) | 88.6 (72.3–96.3) | 80.9 (57.4–93.7) | 100 (86.3–100) | 92.3 |
| 2–3 cm | 100 (59.8–100) | 92.3 (62.1–99.6) | 88.9 (50.6–99.4) | 100 (69.9–100) | 95.2 |

NPV = negative predictive value, PPV = positive predictive value.
95% confidence interval in parentheses.

relevant issue in clinical settings, particularly with different levels of experience between observers. Performance of elastography depends on multiple factors, such as breast size, density, depth and proximity of a lesion to the nipple/areola, making it difficult to achieve consistently optimal image quality for all cases. All these reasons could account for the variability in results in our study. It might be beneficial to address these limitations in larger studies, so that methods could be developed to provide more quantitative elasticity assessment and to further improve the sensitivity and specificity of elastography.

## CONCLUSIONS

Combination of elastography parameters (ES and SR) with conventional ultrasound can increase the probability of proper diagnosis in the case of benign lesions. Implementation of elastography in conventional ultrasound examination should reassure examiners on the use of short-term or routine follow-ups instead of unnecessary biopsies in cases of benign and probably benign lesions.

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