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BREAST IMAGING
ORIGINAL ARTICLE

Use of shear wave elastography to differentiate benign and malignant breast lesions

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PURPOSE
We aimed to determine the correlations between the elasticity values of solid breast masses and histopathological findings to define cutoff elasticity values differentiating malignant from benign lesions.

MATERIALS and METHODS
A total of 115 solid breast lesions of 109 consecutive patients were evaluated prospectively using shear wave elastography (SWE). Two orthogonal elastographic images of each lesion were obtained. Minimum, mean, and maximum elasticity values were calculated in regions of interest placed over the stiffest areas on the two images; we also calculated mass/fat elasticity ratios. Correlation of elastographic measurements with histopathological results were studied.

RESULTS
Eighty-three benign and thirty-two malignant lesions were histopathologically diagnosed. The minimum, mean, and maximum elasticity values, and the mass/fat elasticity ratios of malignant lesions, were significantly higher than those of benign lesions. The cutoff value was 45.7 kPa for mean elasticity (sensitivity, 96%; specificity, 95%), 54.3 kPa for maximum elasticity (sensitivity, 95%; specificity, 94%), 37.1 kPa for minimum elasticity (sensitivity, 96%; specificity, 95%), and 4.6 for the mass/fat elasticity ratio (sensitivity, 97%; specificity, 95%).

CONCLUSION
SWE yields additional valuable quantitative data to ultrasonographic examination on solid breast lesions. SWE may serve as a complementary tool for diagnosis of breast lesions. Long-term clinical studies are required to accurately select lesions requiring biopsy.

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Breast cancer is associated with high morbidity; ~1.38 million new cases and 458 000 deaths occur annually worldwide (1). Breast cancer is by far the most common cancer in females of both developed and developing countries, and remains a major public health problem.

Annual mammographic screening is valuable for early detection of breast cancer, reducing mortality and morbidity, particularly of patients with tumors in fatty breast tissue (2). Increase in breast tissue density over time is a serious problem; this reduces the diagnostic accuracy of breast cancer, especially in younger females (3). Thus, as the proportion of glandular breast tissue rises, other imaging methods are required (4).

Gray-scale ultrasonography is a valuable adjunct to mammography and other breast imaging methods, affording highly sensitive assessment of breast masses and differentiating benign solid breast lesions from those that are malignant (5–7). However, ultrasonography is strongly subjective and poorly specific (8–10).

Breast biopsy remains the gold standard for definitive diagnosis of suspicious breast lesions. Although the total number of females referred for interventional diagnostic procedures represents a small percentage of any screened population, the healthcare resources consumed by such females are disproportionately high (11). Further, the pathological result is benign in up to 75% of all cases (11–13). Therefore, a reliable, noninvasive, costeffective method helping to differentiate benign from malignant breast lesions, thus reducing the number of unnecessary interventional diagnostic procedures, would be valuable.

Sonoelastography uses ultrasound to assess tissue stiffness (elasticity), which can be described using Young's modulus: $E=\sigma/\varepsilon$, where σ is the applied stress and ε the resultant tissue deformation. Two principal sonoelastographic approaches are available; these are static (strain) and transient (vibration; shear wave) elastography. In static elastography, a transducer is used to compress tissue and the resulting strain is presented as a color map of tissue elasticity superimposed on the real-time gray-scale sonogram.

Static elastography is associated with significant interobserver variability, and uses elastographic scoring (ES) or strain ratio (SR) measurement as a diagnostic parameter. Both ES and SR are subjective semi-quantitative measures (14, 15). Shear wave elastography (SWE) is a novel technique applicable to soft tissue. In SWE, transverse shear waves spreading laterally from the tissue are tracked, and the speed of propagation calculated. SWE yields real-time quantitative data and is highly reproducible compared to static elastography (16, 17). Reproducibility of the latter technique is considered to be a major problem and may compromise patient outcomes. Thus, further work on the utility of SWE is needed.

In the present study we sought to correlate the SWE values of a series of solid breast masses with histopathological findings, and to determine cutoff elasticity values allowing benign and malignant tumors to be distinguished.

Materials and methods

Patient selection

This prospective study was performed between January 2012 and December 2012 on 115 lesions of 109 patients (107 females, two males). All patients gave written informed consent to biopsy and use of images. Of all patients, 103 had a single lesion whereas six had two lesions. The age range was 17–87 years and the mean age 51 years. Patients with ultrasonographically identifiable Breast Imaging-Reporting and Data System (BI-RADS) category III, IV, and V solid breast lesions who were referred to our breast radiology department for ultrasonography-guided biopsy were included in the present study. Patients who had undergone any interventional procedure (biopsy, surgery, etc.) to treat a solid breast lesion in the three months prior to biopsy were excluded.

Imaging

Prior to performance of ultrasonographically guided percutaneous biopsy, all patients first underwent gray-scale ultrasound examination and then elastography. Both ultrasonography and sonoelastography were performed by an experienced radiologist (D.Ç.O., eight years of experience). All ultrasound and SWE examinations were performed using a 4-15 MHz linear transducer (SuperSonic Imagine, Aix en Provence, France). During gray-scale ultrasonographic examination, lesion size (length, width, and depth) were measured, and elastography followed. The display presents elastograms overlaid on gray-scale images, assisting in anatomical localization of any mass. SWE was conducted with the aid of a movable intelligent unit displaying tissue stiffness on a color scale; progression from blue to red indicates increasing shear modulus (stiffness). Tissue data were also displayed in kilopascals (kPa), guiding delineation of regions of interest (ROIs). The upper scale limit may be manually adjusted, but a change in limits does not affect measured shear modulus values. We used a lower limit of 10 kPa so that all tissues (including both fatty tissue and a mass) within the rectangular display were red. This was to blind the radiologist (D.Ç.O.) to differences in tissue stiffness while conducting examinations. Two orthogonal elastographic cineloops at least 10 s in duration were obtained. During acquisition, patients were told to breathe slightly and to not move otherwise.

Image analysis

As explained above, D.Ç.O. acquired elastographic data but elastographic measurements were performed by another experienced radiologist (H.Y., 10 years of experience). Both radiologists were blinded to mammographic and clinical findings, and H.Y. was also blinded to ultrasonographic data. H.Y. adjusted the lower limit of the chromatic scale to 180 kPa, to render differences in tissue stiffness evident. Optimum images were chosen from cineloops; these images clearly showed the lesions surrounded by homogenous, poorly elastic, normal, or fatty breast tissue differing in color from that of the lesion. Inbuilt SWE software allowed the operator to delineate circular ROIs of various diameters within the elastographic window, and automatically displayed shear modulus data (in kPa) for each ROI; these included maximum, minimum, and mean values with standard deviations. As each ROI was moved around the image with a cursor, the elastographic values were immediately displayed in a data box, allowing the ROI to be placed in the area of greatest stiffness. We used ROIs 2 mm in diameter. Minimum, mean, and maximum elasticity values were calculated in ROIs placed over the stiffest areas on the color maps, and mass/fat ratios were also determined (Fig. 1). We used breast fat tissue as a comparator because this varies minimally by geographic location, age, hormonal condition, or pathology. The ROI of breast fatty tissue was of the same dimensions as the corresponding breast lesion. The maximum areas of stiffness in malignant lesions were almost always in the peritumoral stroma rather than the lesional centers, and we

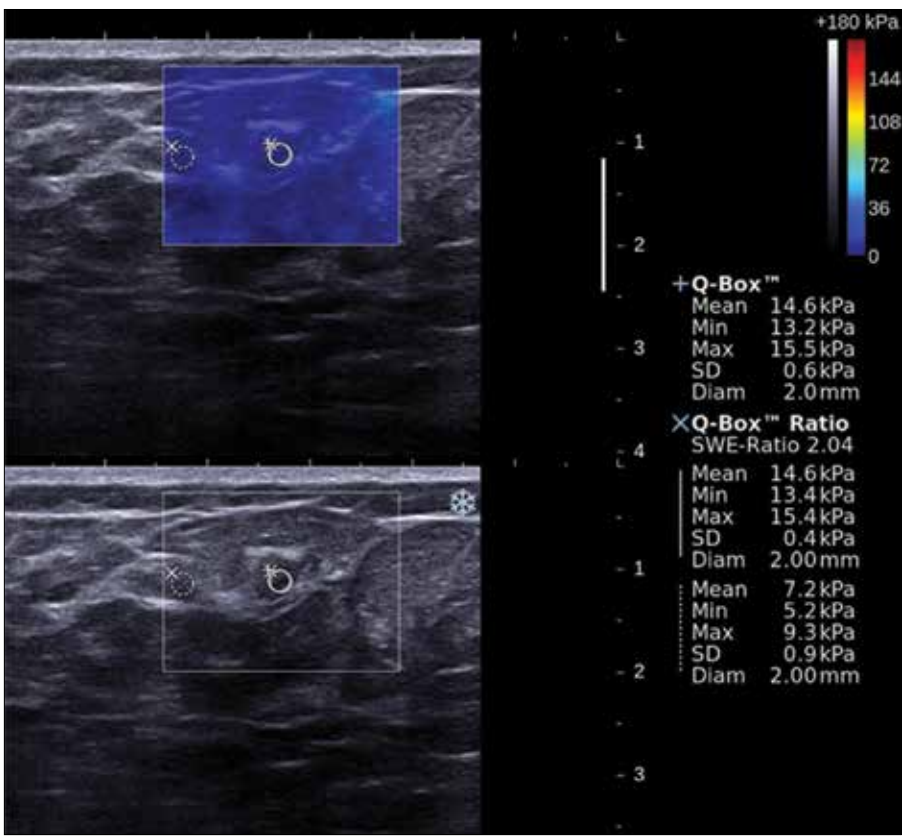

Figure 1. Shear wave elastographic evaluation of a BI-RADS III biopsy-proven fibroadenoma. The B-mode image is shown below the color-coded elasticity map. ROIs were delineated around the stiffest areas on the color maps. All lesions were coded blue during shear wave elastographic ultrasound examination. The ROI of breast fat tissue was of the same size and depth as that of the corresponding lesion. Mean lesion elasticity, 14.6 kPa; mean fat tissue elasticity, 7.2 kPa; mass/fat ratio, 2.04; ROI diameter, 2 mm.

were careful to adequately image these regions (Fig. 2).

Statistical analysis

Statistical analyses were conducted using of the Statistical Package for the Social Sciences (SPSS) (version 19.0 for Windows, SPSS Inc., Chicago, Illinois, USA). Normal data distribution was confirmed using the Kolmogorov-Smirnov method, which also assisted in selection of parametric or nonparametric testing. Differences in lesion size and depth; mean, maximum, and minimum elasticity values; and mass/fat elasticity ratios, among patients with benign and malignant histology, were evaluated using the Mann-Whitney U test. Differences in elastographic data on benign lesions with and without sclerosing components were also evaluated using the Mann-Whitney U test. Elastographic data on malignant lesions were analyzed in an effort to detect differences when the invasive carcinomas varied in terms of histopathological grade.

Receiver operator characteristic (ROC) curves were constructed for the mean, maximum, and minimum elasticity values; and the mass/fat elasticity ratios. The values of these parameters maximizing diagnostic accuracy were obtained, and we calculated sensitivity and specificity values, and negative (NPV) and positive predictive values (PPV).

Results

Totals of 15 (13%) BI-RADS III, 84 (73%) BI-RADS IV, and 16 (14%) BI-RADS V lesions were histopathologically evaluated. Of all lesions, 83 (72%) were benign and 32 (28%) malignant. The most common benign lesion was fibroadenoma (n=48), whereas invasive ductal carcinoma (n=23) was the most common malignant lesion (Table 1).

The mean age of patients with benign histopathological findings was 47.8±12.0 years, and the mean age of those with malignant lesions was 56±12.5 years (P = 0.003). Both the length and width of malignant lesions, were significantly greater than those of benign lesions (longitudinal×transverse: benign, 15×9 mm; malignant, 20×14 mm; both P values < 0.002). Mean lesion depth did not differ significantly (benign, 7.4 mm; malignant, 7.1 mm; $P > 0.05$).

The minimum, mean, and maximum elasticity values, and the mass/fat ratio of benign histopathologic lesions were 19.59 kPa, 25.25 kPa, 31.26 kPa, and 2.43, respectively. All elastographic measures of malignant lesions were significantly higher than those of benign lesions (Table 2).

The areas under the ROC curves were 0.973 for mean elasticity, 0.969 for minimum elasticity, 0.972 for maximum elasticity, and 0.987 for mass/fat elasticity ratio (Fig. 3). The cutoff values affording the maximal predictive accuracy were 37.05 kPa, 45.70 kPa, 54.25 kPa, and 4.70, respectively, for the minimum, mean, and maximum elasticity values, and the mass/fat ratio. The sensitivities, specificities, NPVs, and PPVs derived using these values are summarized in Table 3. The elastographic mass/fat ratio was the most

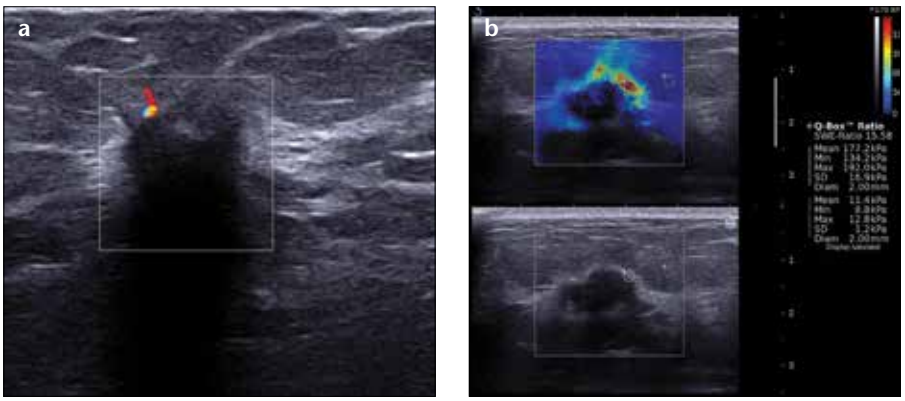

Figure 2. a, b. Gray-scale and color Doppler ultrasonographic evaluation of a BI-RADS V lesion that proved to be a grade II invasive ductal carcinoma **(a)**. Peripheral vascularization was evident on color Doppler imaging. Evaluation via shear wave elastography **(b)** showed that the maximum areas of stiffness were almost always located in the peritumoral stromal regions, and we thus placed the ROIs in these regions. Stiff areas were found only at lesion peripheries, and were coded red-yellow. Lesion centers were almost pure blue in color. The ROI of the breast fat tissue was of the same dimensions as the corresponding lesion. Mean lesional elasticity, 177.2 kPa; mean elasticity of fat tissue, 11.4 kPa; mass/fat ratio, 15.58; ROI diameter, 2 mm.

Table 1. Final histopathologic diagnosis in 115 solid breast lesions

Histopathology	Number of lesions
Malignant histopathology	32
Invasive ductal carcinoma	25
Invasive lobular carcinoma	3
In situ ductal carcinoma	1
Invasive micropapillary carcinoma	1
Mucinous (colloidal) carcinoma	1
Mixed type invasive carcinoma	1
Benign histopathology	83
Neoplastic	55
Fibroadenoma	48
Intraductal papilloma	5
Benign philloides tumor	2
Non-neoplastic	28
Fibrocystic changes	18
Active chronic mastitis	4
Intramammarian lymph node	3
Fat necrosis	3

Table 2. Average gray-scale ultrasonographic and elastographic measurements of benign and malignant lesions

	Benign lesions	Malignant lesions	*P*
Patient age (years)	47.76	56.37	< 0.05
Minimum elasticity value (kPa)	19.59	112.40	< 0.01
Mean elasticity value (kPa)	25.25	156.66	< 0.01
Maximum elasticity value (kPa)	31.26	184.54	< 0.01
Mass/fat elasticity ratio	2.43	11.4	< 0.01
Lesion depth (mm)	7.4	7.09	> 0.05
Lesion size (mm)	15×9	20×14	< 0.05

kPa, kilopascal.

Table 3. Sensitivity, specificity, negative and positive predictive values according to shear wave elastography cutoff values of minimum elasticity 37.05 kPa, mean elasticity 45.70 kPa, maximum elasticity 54.25 kPa, and mass/at ratio 4.70

	Minimum elasticity value	Mean elasticity value	Maximum elasticity value	Mass/fat elasticity ratio
Sensitivity	96.5%	96.5%	96.4%	96.7%
Specificity	95.3%	95.3%	94.3%	96.5%
Negative predictive value	98.8%	98.8%	98.8%	98.8%
Positive predictive value	87.5%	87.5%	84.4%	90.6%

Table 4. Factors affecting shear wave elastography measurements for benign and malignant lesions

	Minimum elasticity value	Mean elasticity value	Maximum elasticity value	Mass/fat elasticity ratio
Benign lesions				
Sclerosing component				
Present (n=5)	36.46 kPa	46.24 kPa	53.34 kPa	3.57
Absent (n=78)	18.51 kPa	23.90 kPa	29.84 kPa	2.35
P	0.082	0.042	0.087	0.034
Malignant lesions				
Histological grade of the lesion				
Grade 1 (n=3)	50.40 kPa	64.30 kPa	74.1 kPa	5.62
Grade 2–3 (n=28)	116.80 kPa	162.5 kPa	191.1 kPa	11.68
P	0.026	0.013	0.010	0.061

useful parameter, with a sensitivity of 97%, a specificity of 95%, a PPV of 88%, and an NPV of 99%. When the cutoff values for mean elasticity and mass/fat elasticity ratio were combined, the sensitivity became 96%, the specificity 91%, the PPV 91%, and the NPV 99%.

Sclerosing adenosis is difficult to define pathologically. The mean elasticity and mass/fat elasticity ratio were significantly higher for benign lesions with than without sclerosing components ($P < 0.03$) (Fig. 4, Table 4). Lesions with sclerosing components were sclerosing intraductal papilloma, sclerosing adenosis, and fibroadenoma with sclerosing adenosis.

We observed that the elasticity values of malignant lesions varied by lesional grade ($P < 0.02$). Low-grade lesions (ductal carcinoma *in situ* and grade 1 lesions) had lower minimum, mean, and maximum elasticity values than did high-grade lesions (Fig. 5, Table 4).

Discussion

We have shown that several shear wave elastographic parameters, including the minimum, mean, and maximum elasticity values, and the mass/fat ratio, can be used to differentiate benign from malignant solid breast lesions. SWE differs from conventional elastography in that the former technique yields quantitative data and appears to be more reproducible and objective (16). In the present work, the most useful and reproducible measure was the mass/fat elasticity ratio, unlike what was found by Wang et al. ($P < 0.01$ vs. $P = 0.088$) (18). Breast fat tissue shows minimal elastographic variability, and the elasticity values are very low, supporting the use of fat tissue stiffness as a comparator (16, 19). Probe compression raises elastographic values, increasing the likelihood of overdiagnosis. The mass/fat elasticity ratio is not influenced by compression because breast fat tissue and the lesion are subjected to the same pressure.

Lesion heterogenity which was evident upon gray-scale ultrasonography has been used to differentiate benign from malignant breast masses. Evans et al. (16) suggested that elastographic standard deviation was a useful measure of heterogeneity, differentiating benign from malignant lesions, because the value was significantly higher in patients with malignant histopathology. The maximum elasticity values of malignant lesions were almost always associated with the peritumoral stroma rather than the centers of the lesions, and may reflect a combination of unresolved spiculation and a surrounding desmoplastic reaction (20, 21). Also, the centers of some lesions did not yield measures of shear elastic modulus. Thus, it is sometimes impossible to obtain data from an entire lesion. We suggest that standard deviations do not reflect the heterogeneity of the entire lesion because, in shear wave elastography, the values are obtained from a fixed ROI, generally the stiffest peritumoral area. If it were important to explore lesion heterogeneity, freehand ROI drawing techniques would be required, but are not yet available.

The mean elasticity cutoff value yielding the maximum sum of specificity and sensitivity was 45.70 kPa, whereas Evans

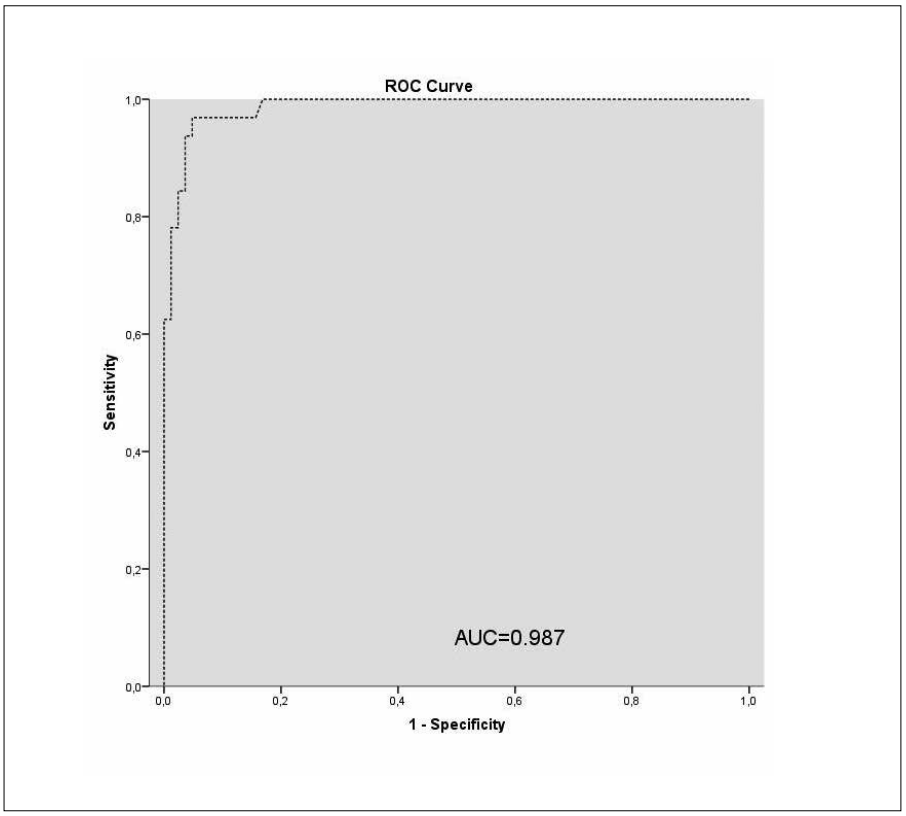

Figure 3. Receiver operating characteristic (ROC) curve of the mass/fat elasticity ratio. AUC, area under curve.

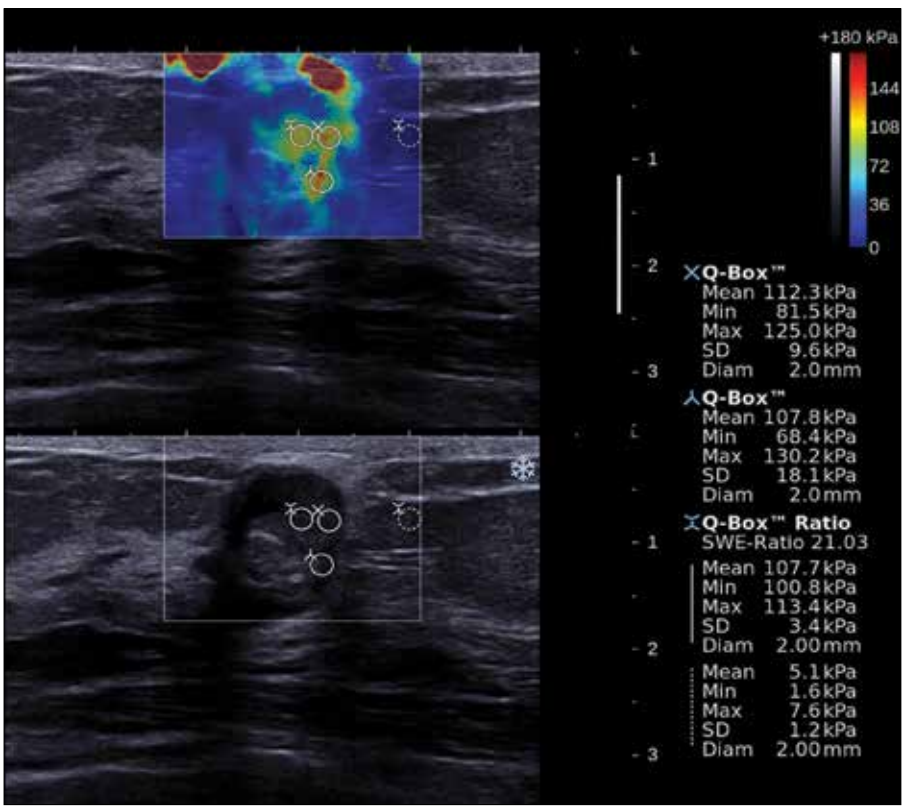

Figure 4. Shear wave elastographic evaluation of a BI-RADS IV biopsy-proven sclerosing intraductal papilloma. The peripheral regions of the lesion (yellow) had a mean elasticity of 112 kPa. Maximum elasticity value of the lesion, 125 kPa; minimum elasticity value of the lesion, 81.5 kPa; mean elasticity value of fatty tissue, 5.1 kPa; mass/fat ratio, 21.03; ROI diameter, 2 mm. Areas coded red reflect probe compression of the skin.

et al. (16) and Chang et al. (22) calculated mean elasticity cutoff values of 50 kPa and 80.17 kPa, respectively. In our present study, the mean elasticity cutoff value was associated with a sensitivity, a specificity, an NPV, and a PPV of 97%, 95%, 99%, and 88%, respectively. We found that elasticity measures differentiated benign from malignant lesions more effectively than noted by Evans et al. (16) (sensitivity, 97%; specificity, 83%; NPV, 95%; and PPV, 88%) and Chang et al. (22) (sensitivity, 89%; specificity, 85%; NPV, 89%; and PPV, 85%). The publication of more data in the intervals since the cited reports appeared, and use of a standardized examination protocol, may explain our better results.

Interestingly, the histopathological grades of invasive cancers (and of sclerosing components of breast lesions) were significantly associated with shear wave elastographic measures. This finding is in line with those of recent studies showing relationships between shear wave elastographic findings and histological prognostic factors (23, 24). A higher histological grade was associated with a higher mean stiffness in both cited studies. In the present study, we also found that higher-grade lesions had higher minimum and maximum elasticity values. High-grade breast lesions tend to exert stronger desmoplastic effects on peritumoral tissues. The numbers of mitoses increased, reflecting enhanced cellularity and an excessive desmoplastic reaction, explaining why a high-grade cancer may exhibit high stiffness values (25). Further, low-grade malignant lesions and benign lesions with sclerosing components tend to yield to false-negative and false-positive results, respectively. This shows that malignant and benign breast lesions exhibit overlapping features, as reported in previous studies (16, 18, 22, 26).

Our study had some limitations. First, our patient series was relatively small, but we suggest that the experiences of other centers will confirm our findings. Second, not all histological types of malignant and benign lesions were represented. Multicenter prospective studies are needed to overcome this limitation. Third, we did not assess interobserver variability but the method has been shown previously to be highly reproducible (16, 17).

In conclusion, although biopsy remains the gold standard for diagnosis

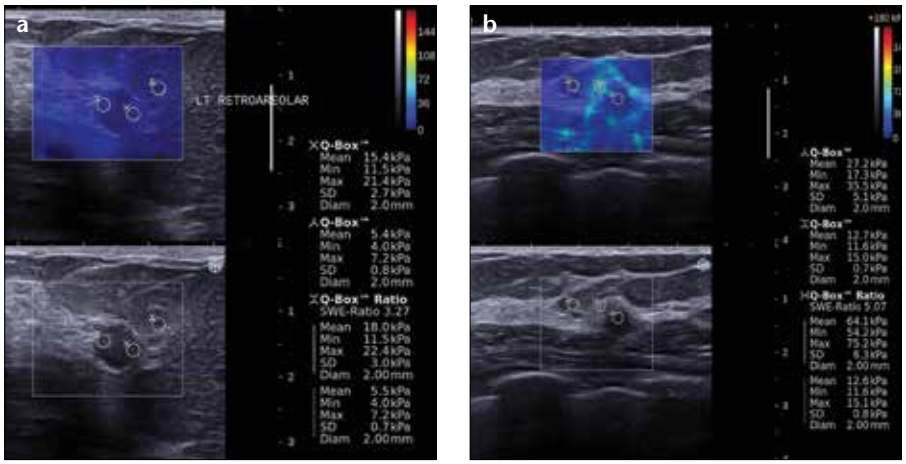

Figure 5. a, b. Shear wave elastographic examination of two BI-RADS IV lesions that proved to be grade 1 invasive ductal carcinoma. Upon shear wave elastographic ultrasound examination, both lesions were blue **(a)**. Mean elasticity value of the lesion, 18 kPa; maximum elasticity value of the lesion, 22.4 kPa; minimum elasticity value of the lesion, 11.5 kPa; mean elasticity value of fatty tissue, 5.5 kPa; mass/fat ratio, 3.27; ROI diameter, 2 mm. This was the only false-negative case encountered. Stiff areas were found only in the periphery of the lesion and are coded green **(b)**. Mean elasticity value of the lesion, 64.1 kPa; maximum elasticity value of the lesion, 75.2 kPa; minimum elasticity value of the lesion, 54.2 kPa; mean elasticity value of fatty tissue, 12.6 kPa; mass/fat ratio, 5.07; ROI diameter, 2 mm.

of suspicious breast lesions, a large proportion of biopsy specimens is benign. Therefore, a noninvasive and reliable method identifying low-risk lesions, and reducing unnecessary interventional diagnostic procedures, would be valuable. SWE provides quantitative elasticity information that can facilitate characterization of breast lesions. Further large-scale studies and future advances in shear wave imaging will allow SWE to contribute to accurate selection of lesions requiring biopsy and may potentially be used for real-time guidance when biopsies of suspicious foci are underway.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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