Potential of Lesion-to-Fat Elasticity Ratio Measured by Shear Wave Elastography to Reduce Benign Biopsies in BI-RADS 4 Breast Lesions

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Abbreviations

2Dtwo-dimensional; ACRAmerican College of Radiology; AUCarea under the curve; BI-RADSBreast Imaging Reporting and Data System; ROC, receiver operating characteristic; SE, strain elastography; SWE, shear wave elastography

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Objectives—We evaluated whether lesion-to-fat ratio measured by shear wave elastography in patients with Breast Imaging Reporting and Data System (BI-RADS) 3 or 4 lesions has the potential to further refine the assessment of B-mode ultrasound alone in breast cancer diagnostics.

Methods—This was a secondary analysis of an international diagnostic multicenter trial (NCT02638935). Data from 1288 women with breast lesions categorized as BI-RADS 3 and 4a–c by conventional B-mode ultrasound were analyzed, whereby the focus was placed on differentiating lesions categorized as BI-RADS 3 and BI-RADS 4a. All women underwent shear wave elastography and histopathologic evaluation functioning as reference standard. Reduction of benign biopsies as well as the number of missed malignancies after reclassification using lesion-to-fat ratio measured by shear wave elastography were evaluated.

Results—Breast cancer was diagnosed in 368 (28.6%) of 1288 lesions. The assessment with conventional B-mode ultrasound resulted in 53.8% (495 of 1288) pathologically benign lesions categorized as BI-RADS 4 and therefore false positives as well as in 1.39% (6 of 431) undetected malignancies categorized as BI-RADS 3. Additional lesion-to-fat ratio in BI-RADS 4a lesions with a cutoff value of 1.85 resulted in 30.11% biopsies of benign lesions which correspond to a reduction of 44.04% of false positives.

Conclusions—Adding lesion-to-fat ratio measured by shear wave elastography to conventional B-mode ultrasound in BI-RADS 4a breast lesions could help reduce the number of benign biopsies by 44.04%. At the same time, however, 1.98% of malignancies were missed, which would still be in line with American College of Radiology BI-RADS 3 definition of <2% of undetected malignancies.

Key Words—B-mode ultrasound; biopsy; breast cancer diagnostics; shear wave elastography

Supplementary breast ultrasound in addition to mammography has improved diagnostic accuracy of breast cancer diagnostics by detection of mammographically occult lesions.[1,2] Breast lesions are categorized depending on their

probability of malignancy by the Breast Imaging Reporting and Data System (BI-RADS).[3] Key point in breast cancer diagnostics is the differentiation between lesions that are categorized as BI-RADS 3 (likelihood of malignancy under 2%) and BI-RADS 4 (2–95% likelihood of malignancy), especially BI-RADS 4a (2%–10% likelihood of malignancy).[4] Whereas patients with lesions categorized as BI-RADS 3 are recommended to undergo a short-term follow-up, those with lesions categorized as BI-RADS 4 are recommended to receive a biopsy.[5,6] These settings result in about 2% of initially undetected breast cancers in the BI-RADS 3 cohort and in up to 90% benign biopsies in the BI-RADS 4a cohort.[7,8] The main challenge of breast cancer diagnostics is therefore to perform histopathologic confirmation by biopsy in as many patients as necessary but in as few as reasonably achievable. Additional tools are needed to better differentiate between lesions to biopsy and lesions to follow-up.

One potential technique might be two-dimensional (2D) shear wave elastography (SWE) that provides sonographic quantification of tissue stiffness based on shear-wave velocity.[9] Increased tissue stiffness is a known predictor for malignancy and is already an established complementary tool in breast cancer diagnostics since its implementation in BI-RADS classification.[10–14] SWE quantifies the stiffness of a lesion by evaluating the propagating speed of shear waves through the tissue.[15] Increased tissue stiffness is a known predictor for malignancy. High stiffness is reported to be due to high levels of collagen, myofibroblasts, angiogenesis, inflammatory reaction, necrosis, and different tumor histologic biomarkers.[16,17] SWE has shown promising results in breast diagnostics, as average values of stiffness for fatty, benign glandular, and malignant glandular breast tissue have been established.[18,19] Although SWE showed great potential to reduce false-positive findings on B-mode breast ultrasound (reducing benign biopsies), it misses some cancers detected on B-mode breast ultrasound (even when combined with strain elastography).[13,20,21] Lesion-to-fat-ratio, which compares the SWE velocity in the lesion to the SWE velocity in the surrounding fatty tissue, is proposed as a more sensitive measure. No prospective study has yet evaluated the potential of lesion-to-fat ratio measured by SWE in breast cancer diagnostics.[22,23] In this secondary analysis of a prospective, multicenter trial, we aimed to evaluate whether additional lesion-to-fat ratio measured by SWE for patients with BI-RADS 3 or 4 lesions on breast ultrasound could further refine the assessment with B-mode breast ultrasound for breast cancer diagnosis.

Materials and Methods

Patient Population

Secondary outcomes of a prospective, multicenter, diagnostic trial are reported. The trial was conducted at 12 sites in seven countries (Austria, France, Germany, Japan, Portugal, the Netherlands, and the United States) from 2016 to 2019. The trial consecutively enrolled women who presented with a lesion ≥0.5 and ≤5 cm in thelargest diameter size that was initially scored as BI-RADS 3, 4a, 4b, or 4c in 2D B-mode ultrasound. All patients received SWE and subsequently underwent histopathologic confirmation. Exclusion criteria were a history ofbreast cancer or breast surgery in the same quadrant or lesionsthat have been previously biopsied. Only one lesion per patientwas included. The trial was registered on ClinicalTrials.gov (NCT02638935) and approved by all respective ethical committees. In addition, written informed consent was obtained by all participating patients.

SWE Measurement

All participating patients underwent routine 2D B-mode ultrasound examination of the breast. All findings were categorized according to the American College of Radiology (ACR) BI-RADS classification, 5th edition, using a 18 MHz linear transducer (Siemens ACUSON S2000). All patients received SWE measurements as part of the study using a 9 MHz linear transducer (Siemens ACUSON S2000). The SWE measurement was performed three times by a board-certified specialized physician in breast diagnostics within the lesion whereby the region with the highest velocity within the target lesion was defined as region of interest. After that, SWE measurement of the surrounding fatty tissue was performed in the same penetration depth as the measurement in the lesion within the same SWE image. There was no restriction regarding the

distance to the lesion. All SWE measurements were performed before histopathologic examination.

Study Design and Outcome Measures

The aim of this secondary analysis of the study was to evaluate the added value of lesion-to-fat ratio measured by SWE in addition to routine 2D B-mode ultrasound in the correct classification of breast lesions categorized as BI-RADS 3 or 4a–c, whereby the focus was placed on BI-RADS 3 and 4a. Final histopathologic evaluation served as reference standard. The results of the SWE measurement had no effect on patient care in context of this study. Outcome measures were the proportion of undetected malignancies in the BI-RADS 3 cohort as well as the proportion of benign biopsies in the BI-RADS 4a–c cohort with histologic benign lesions before and after the performance of additional lesion-to-fat ratio by SWE to standard B-mode ultrasound. As the standard recommendation for BI-RADS 3 lesions is short-term follow up, only patients who received a biopsy or a surgical excision due to patient's request were included to this study. The histopathologic examination was performed at the respective study site as part of the clinical routine. The respective pathologists were blinded for information regarding SWE measurements.

Statistical Analysis

Baseline und tumor characteristics were described using descriptive measures. Continuous variables were expressed as mean ± SD and categorical variables as absolute and relative frequencies. In addition, the number of missing values was added (if present).

To evaluate the potential use of lesion-to-fat ratio measured by SWE for correct classification of breast lesions categorized as BI-RADS 3 or 4a–c, three different approaches to determine the SWE cutoff were evaluated. First, a SWE cutoff that resulted in the same number of undetected malignancies as B-mode breast ultrasound after re-classification with SWE and strain elastography (SE) was determined. Second, a SWE cutoff that resulted in a maximum of 2% undetected malignancies (analogous to the ACR BI-RADS 3 definition) after reclassification was determined. Third, receiver operating characteristic (ROC) curves were used as SWE cutoff determination dividing malignant and benign tumors and considered optimal when the point on the ROC curve is closest to (0,1). Specificity, sensitivity (for the optimal cutoff), and area under the curve (AUC) were provided additionally.

The mean of the three lesion-to-fat-ratio measurements was used for the analyses. The rate of undetected malignancies (malignant lesions in BI-RADS 3) and the rate of unnecessary biopsies (biopsies in benign lesions in BI-RADS 4) for the assessment with B-mode breast ultrasound and after reclassification with lesion-to-fat ratio were then calculated for both approaches and compared against each other.

Statistical analyses were conducted using the statistic software R (version 4.1.2, R Core Team, Auckland, New Zealand) using the packages "cutpointr" for ROC analysis "ggplot" for data illustrations.

Results

Patient Population

A total of 1288 women underwent routine B-mode ultrasound of the breast as well as SWE measurement in lesion and fatty tissue of the breast followed by histopathologic examination. Details on this study population are published elsewhere.[13] Mean age was 46.49 ± 16.05 years and 368 (28.57%) of all lesions showed malignancy in the histopathologic examination.

Routine B-Mode Ultrasound and Histopathologic Examination

Following routine B-mode ultrasound 33.46% of all lesions were categorized as BI-RADS 3 (n = 431), 34.39% as BI-RADS 4a (n = 443), 14.52% as BI-RADS 4b (n = 187), and 17.62% as BI-RADS 4c (n = 227), respectively. This resulted in 53.80% benign biopsies (495 of 920) in all lesions classified as BI-RADS 4a–c as well as 1.39% undetected breast cancers (6 of 431) in all lesions classified as BI-RADS 3. Malignancy rate and the rate of benign biopsies of the respective categories are shown in Table 1.

SWE in Lesion and Fatty Tissue

Mean values for the average of the three SWE measurement of each patient in lesion, fatty tissue and lesion-to-fat ratio were 4.18 ± 2.20 m/s,

1.94 ± 0.66 m/s, and 2.22 ± 1.07, respectively (Table 2).

ROC Analysis

To determine the optimal cutoff point of the lesion-to-fat ratio to differentiate between benign and malignant lesions, the ROC curve was used, whereby the cutoff point closest to the point (0,1) was considered optimal. Figure 1 illustrates the optimal cutoff point at 2.14 with a sensitivity of 0.75 and a specificity of 0.77 and AUC of 0.8258. Calculating with the optimal cutoff of 2.14 reclassification of BI-RADS 3 to 4c would result in a rate of benign biopsies ranging from 19.02% to 32.93% (depending on the specific BI-RADS categories that were recategorized), corresponding to a reduction in benign biopsies ranging from 38.79% to 64.65%. This would come at the expense of additionally missed cancers between 2.75% and 11.20%, depending on the BI-RADS category (Table 3).

When lesion-to-fat ratio was set so that B-mode ultrasound and lesion-to-fat ratio missed the same number of cancers (n = 6), the reclassification of BI-RADS 4a would result in a reduction of benign biopsy of 7.27% (459 versus 495) with a cutoff value of 1.15. Reclassification of BI-RADS 3 + 4a, BI-RADS 3 + 4a + b, and BI-RADS 3 + 4a–c would have resulted in an increase of benign biopsy of 8.69%, 49.90%, and 70.51% (538, 742, and 844 versus 495), respectively (Table 3).

When lesion-to-fat ratio was set so that B-mode ultrasound and lesion-to-fat ratio missed ≤2% of cancers according to the definition by ACR BI-RADS of

Figure 1. ROC analysis.

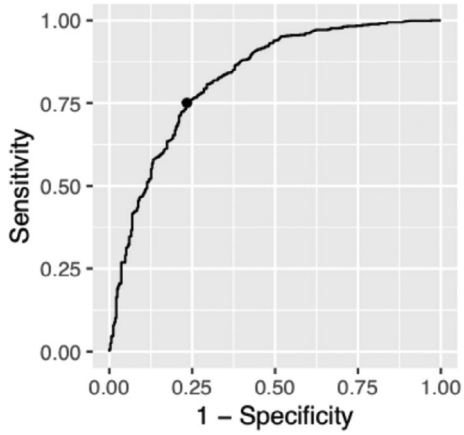

Table 1. Absolute and Relative Frequencies of Malignancy and Benign Biopsies Following B-Mode Breast Ultrasound

	BI-RADS 3 (n = 431)	BI-RADS 4a (n = 443)	BI-RADS 4b (n = 187)	BI-RADS 4c (n = 227)
Malignancy	6 (1.39%)	44 (9.93%)	111 (59.36%)	207 (91.19%)
Benign biopsies	0 (0%)	399 (90.07%)	76 (40.64%)	20 (8.81%)

Table 2. Mean of the Three Measured Velocities in Lesion and Fatty Tissue as Well as Lesion-to-Fat Ratio Using Mean ± Standard Deviation as Well as Number of Missing Values

	BI-RADS 3 (n = 431)	BI-RADS 4a (n = 443)	BI-RADS 4b (n = 187)	BI-RADS 4c (n = 227)	Total (n = 1288)
Lesion (m/s)					
Total	3.21 ± 1.24 (3)	3.66 ± 1.91 (2)	5.06 ± 2.17 (1)	6.35 ± 2.47 (5)	4.18 ± 2.20 (11)
Benign	3.21 ± 1.24 (3)	3.48 ± 1.73 (2)	4.35 ± 1.78 (0)	4.93 ± 2.22 (0)	3.46 ± 1.58 (5)
Malignant	3.24 ± 0.97 (0)	5.29 ± 2.59 (0)	5.55 ± 2.28 (1)	6.49 ± 2.46 (5)	6.00 ± 2.47 (6)
Fatty tissue (m/s)					
Total	1.92 ± 0.58 (22)	1.85 ± 0.66 (36)	2.04 ± 0.71 (23)	2.09 ± 0.72 (10)	1.94 ± 0.66 (91)
Benign	1.92 ± 0.58 (22)	1.85 ± 0.67 (33)	2.18 ± 0.88 (8)	2.09 ± 0.55 (3)	1.92 ± 0.65 (66)
Malignant	1.90 ± 0.58 (0)	1.85 ± 0.57 (3)	1.95 ± 0.55 (15)	2.09 ± 0.73 (7)	2.02 ± 0.67 (25)
Lesion-to-fat ratio					
Total	1.75 ± 0.56 (26)	1.99 ± 0.80 (44)	2.04 ± 0.71 (23)	2.67 ± 1.14 (18)	2.22 ± 1.07 (115)
Benign	1.74 ± 0.56 (26)	1.89 ± 0.66 (41)	2.18 ± 1.01 (10)	2.58 ± 1.23 (3)	1.86 ± 0.68 (80)
Malignant	1.79 ± 0.46 (0)	2.87 ± 1.27 (3)	3.01 ± 1.11 (17)	3.32 ± 1.36 (15)	3.15 ± 1.29 (35)

Velocities are given in m/s; the number of missing values is given in parentheses.

BI-RADS 3, the reclassification of BI-RADS 4a with a lesion-to-fat ratio of 1.85 would result in 1.98% of missed cancers (n = 13) and a reduction of benign biopsy of 44.04% (277 versus 495). The reclassification of BI-RADS 4a + b with a lesion-to-fat ratio of 1.30 would result in 1.96% of missed cancers (n = 10) and a reduction of benign biopsy of 14.95% (421 versus 495). Reclassification of BI-RADS 3 + 4a, 3 + 4a–b resulted in an increase of benign biopsies (Table 3).

Discussion

Secondary outcomes of a prospective, international, multicenter diagnostic trial are reported. The diagnostic performance of SWE has been evaluated in previous studies.[24] Golatta et al proposed in the primary analysis of this study population SWE with a cutoff value of 2.55 m/s to downstage BI-RADS 4a lesions into follow-up. SWE showed the potential to thereby reduce biopsies in benign lesions of up to 24%.[13] In lesions categorized other than BI-RADS 4a the addition of SWE showed no/a substantially lower benefit in reducing benign biopsies or detecting additional malignancies. SE is another technique of elastography. Its potential to ameliorate the performance of breast cancer diagnostics in addition to conventional B-mode ultrasound examination was also investigated in multiple studies. It could be shown that both SWE and SE as well as the combination of both techniques can improve diagnostic sensitivity of conventional B-mode ultrasound but mostly at the expense of specificity.[20,25,26] It has not yet been conclusively determined which elastography method provides the best results in breast cancer diagnostics and improves both the sensitivity and specificity of conventional B-mode ultrasound.

Lesion-to-fat ratio is an additional tool offered by SWE to potentially reclassify breast lesions. This study adds to the growing field of evidence analyzing the use of lesion-to-fat ratio in an international multicenter cohort. Aim of this analysis was to explore the ability of lesion-to-fat ratio measured by SWE to better categorize breast lesions according to ACR BI-RADS. Lesions of interest were breast masses

Table 3. Rate of Undetected Malignancies and Benign Biopsies of Different Cutoff Approaches for Reclassification of Breast Lesions Categorized as BI-RADS 3 or 4a–c

Recategorization	Undetected Malignancies	Benign Biopsies	Reduction of Benign Biopsies
B-mode ultrasound	1.39% (6/431)	53.80% (495/920)	
Additional lesion-to-fat ratio with preserved number of undetected malignancies (n = 6)			
BI-RADS 4a to 3 at cutoff 1.15	1.28% (6/467)	49.89% (459/920)	7.27% (459 vs 495)
BI-RADS 4a + b to 3 at cutoff 0.99	1.33% (6/451)	51.63% (475/920)	4.04% (475 vs 495)
BI-RADS 3 to 4 and 4a to 3 at cutoff 1.67	1.55% (6/388)	54.48% (538/920)	-8.69% (increase, 538 vs 495)
BI-RADS 3 to 4 and 4a + b to 3 at cutoff 1.32	3.26% (6/184)	80.65% (742/920)	-49.90% (increase, 742 vs 495)
BI-RADS 3 to 4 and 4a–c to 3 at cutoff 1.12	7.32% (6/82)	91.74% (844/920)	−70.51%, increase (844 vs 495)
Additional lesion-to-fat ratio with rate of undetected malignancies <2%			
BI-RADS 4a to 3 at cutoff 1.85	1.98% (13/656)	30.11% (277/920)	44.04% (277 vs 495)
BI-RADS 4a + b to 3 at cutoff 1.30	1.96% (10/509)	45.76% (421/920)	14.95% (421 vs 495)
BI-RADS 3 to 4 and 4a to 3 at cutoff 1.68	1.78% (7/394)	57.93% (533/920)	−7.68%, increase (533 vs 495)
BI-RADS 3 to 4 and 4a + b to 3 at cutoff 1.03	1.92% (1/141)	94.46% (869/920)	−75.56%, increase (869 vs 495)
BI-RADS 3 to 4 and 4a–c to 3	No cutoff available		
Additional lesion-to-fat ratio with cutoff 2.14 as proposed by the ROC analysis			
BI-RADS 4a to 3	2.75% (20/726)	23.26% (214/920)	56.77% (214 vs 495)
BI-RADS 4a + b to 3	6.05% (48/793)	19.02% (175/920)	64.65% (175 vs 495)
BI-RADS 3 to 4 and 4a to 3	2.83% (18/635)	32.93% (303/920)	38.79% (303 vs 495)
BI-RADS 3 to 4 and 4a + b to 3	6.55% (46/702)	28.70% (264/920)	46.67% (264 vs 495)
BI-RADS 3 to 4 and 4a–c to 3	11.20% (84/750)	27.62% (254/920)	48.69% (254 vs 495)

categorized as BI-RADS 3 or 4a–c by conventional B-mode ultrasound with focus on BI-RADS 3 and 4a lesions. Attention was drawn to the question if additional lesion-to-fat ratio measured by SWE could refine classification to BI-RADS 3 and 4a–c and thereby reduce benign biopsies. The proportion of missing values in the measurement of the velocity of the surrounding fatty tissue is most likely due to the fact that the documentation of SWE in the fatty tissue was not a mandatory measurement in the main study.

In this cohort lesion-to-fat ratio with a cutoff of 1.85 reduced benign biopsies by 44.04%, while the rate of undetected malignancies would still be coherent to ACR BI-RADS classification of BI-RADS 3 (1.98%, 13 cases). Extension of the cutoff of 1.85 to other BI-RADS categories showed no benefit in terms of reduction of benign biopsies or detection of additional malignancies while using ROC analysis the optimal cutoff value of 2.14 reduced benign biopsies in all BI-RADS categories by 48.69% but at the expense of additional missed malignancies of up to 11.20%.

In the literature there are only a few studies reporting on lesions-to-fat ratio measured by elastography in breast lesions. It has been demonstrated that lesion-to-fat ratio is higher in malignant lesions compared to benign lesions (5.37 ± 1.63 versus 3.97 ± 1.33).[23,27] In this study by Chee et al, only 39 patients were enrolled so that selection bias cannot be ruled out. Furthermore, it is noteworthy in this context that the mean values of the lesion-to-fat ratios were higher in both benign and malignant findings. The differences between malignant and benign lesions are again similar (1.29 in the present study and 1.4 in the study by Chee et al).[23] This could be due to the low number of cases in the study by Chee et al or to technical differences. Li et al reported a diagnostic performance of lesion-to-fat ratio that was inferior to that of SWE alone in terms of detection probability of malignant lesions.[28] Ikeda et al showed a reduction of 57.5% of biopsies in benign breast lesions categorized as BI-RADS 3 and 4, whereby the number of missed malignancies was not reported.[29] The result of this study indicates that lesion-to-fat ratio is a useful tool in downstaging BI-RADS 4a breast lesions while women with BI-RADS 3, 4b, or 4c lesions would rather not benefit. The potential to reduce benign biopsies was higher for lesion-to-fat ratio measured by SWE compared with SWE alone or with the combination of SWE and SE.[20,21,30]

A limitation of lesion-to-fat ratio is the question of the right area of measurement. It is not yet defined which localization regarding depth, distance to the lesion, as well as to the skin yields the most accurate ratio.[31] In this cohort measurement in fatty tissue was obtained in the same penetration depth as the lesion, there was no restriction regarding the distance to the lesion. It is also possible that SWE measurement was performed in glandular tissue rather than in adipose tissue, depending on breast density, with measurements in glandular tissue being associated with lower diagnostic performance.[22,23]

Another limitation of this study population is the inclusion of histologically confirmed BI-RADS 3 lesions only. Therefore, a selection bias cannot be ruled out.

This study evaluated hypothetical risk assessments with lesion-to-fat ratio as an additional method to routine B-mode ultrasound. The actual impact of lesion-to-fat ratio has yet to be investigated in future studies, where the results of the lesion-to-fat ratio are implemented in clinical decision making regarding histopathologic confirmation.

Lesion-to-fat ratio measured by SWE with a cutoff of 1.85 could be used to downstage lesions that are categorized as BI-RADS 4a to follow-up. Benign biopsies could be reduced up to 44.04% while the rate of undetected malignancies is still in line with the ACR BI-RADS definition of BI-RADS 3. These results show that lesion-to-fat ratio has a higher potential in differentiating benign and malignant breast lesions as an additional tool to conventional B-mode ultrasound.

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