Original Article

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Evaluation of Strain and Shear Wave Ultrasound Elastography in Predicting Malignancy in BI-RADS Categories 4A and 4B Breast Lesions

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Abstract:

Objective: To evaluate elasticity (E) and optimal cut-off values in differentiating benign and malignant tumors in patients with breast imaging–reporting and data system (BI-RADS) 4A/4B lesions.

Material and Methods: Patients aged above 18 years with BI-RADS 4A/4B lesions who had tissue biopsies November 2019 - January 2021 were enrolled. B-mode ultrasound BI-RADS classification, E/B distance ratio, and mean elasticity value in kPa and shear wave velocity (SWV) in m/s were recorded pre-biopsy.

Results: A total of 148 lesions in 141 patients were included, 129 benign (87.2%), 3 high-risk (2.0%), and 16 malignant (10.8 %). Patients with breast cancer or high-risk lesions were approximately ten years older than those with benign lesions (58.9±10.5 years vs 48±10.6 years of age) (p-value<0.001). The elasticity values were significantly different between the benign and malignant groups with median E/B distance ratios 0.9 and 1.2 (p-value<0.001), median kPa_{mean}s 4.2 and 7.2, and SWV_{mean}s 1.2 m/s and 1.6 m/s, respectively. Setting SWV_{mean} ≥1.28 m/s as a cut-off value showed the highest sensitivity (68.0%) among the three single elasticity values, and kPa_{mean} ≥7 the highest specificity (82.0%). The negative predictive value was very high, 91.0–93.0%, for all methods. When using a combined E/B ratio ≥1 and SWV_{mean} ≥1.28 as a cut-off value, specificity increased to 93.0% with a high NPV but lower sensitivity.

Conclusion: Using a combined E/B ratio ≥1 and SWV_{mean} ≥1.28 as a cut-off value can help to differentiate between benign and malignant BI-RADS 4A and 4B lesions and avoid unnecessary biopsies.

Keywords: benign breast lesion elasticity, BI-RADS 4A and 4B breast lesions, breast lesion elasticity, breast ultrasound elastography, malignant breast lesion elasticity

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Introduction

Breast cancer is the most common cancer in women worldwide, with 2,261,419 new cases and 684,996 deaths in 2020.[1] While the screening mammogram has proved to be an effective tool for early detection of breast cancer, supplemental ultrasound detects 2-3 more cancers per 1,000 patients, especially in mammographically dense breasts.[2] However, ultrasound also has higher false-positive rates, resulting in an increased number of biopsies, especially in breast imaging–reporting and data system (BI-RADS) 4A and 4B lesions.[3] Previous studies have suggested that ultrasound elastography can help in differentiation between benign and malignant lesions when combined with B-mode ultrasound.[4] The two main methods of elastography are strain and shear wave imaging; the diagnostic performance of the two methods is similar.[4,5] A recent study found that combining these two methods improved the sensitivity significantly and decreased the risk of downgrading breast cancers.[6]

Our institutional breast center sees more than 700 patients per year diagnosed with BI-RADS 4A and/or 4B for biopsy. Most of the lesions are recommended for biopsy based on B-mode ultrasound alone. Biopsy data from the year prior to this study showed 93.5% and 80.0% benign for BI-RADS 4A and 4B, respectively. Therefore, this study's purpose was to evaluate the elasticity values and the optimal cut-off values for differentiating benign and malignant breast lesions in patients with BI-RADS 4A and 4B lesions. The study also examined if elastography could accurately downgrade BI-RADS 4A lesions while still avoiding missing true cancers.

Material and Methods

This prospective study received approval from the Institutional Review Board (REC. 62-403-7-4). All patients aged above 18 years with BI-RADS 4A or 4B lesions who received a tissue biopsy during November 2019 - January 2021 were eligible to be included in the study. The exclusion criteria were patients with an ipsilateral breast implant or surgery, currently receiving treatment for any cancer, pregnant or lactating, or mass larger than 3 cm in diameter, deeper than 3 cm in depth, or located too superficially for an imaging box to cover. Patients meeting the inclusion criteria provided written informed consent before being enrolled in the study.

Each patient's B-mode ultrasound BI-RADS classification was assigned using a combination of mass shape, margin, orientation, echo pattern, posterior features, and vascularity. The ultrasound elastographies were performed using a Siemens Acuson Sequoia ultrasound system by a subspecialist in breast radiology with 10 years experience and/or one clinical fellow subspecializing in breast imaging. Both strain and shear wave elastography (SWE) were performed using a 10L4 linear transducer probe with Acoustic Radiation Force Impulse (ARFI) technology. The intra-class correlation coefficient (ICC) between the two radiologists was 0.857 for median kilopascals (kPa_{median}), 0.815 for median shear wave velocity (SWV_{median}), and 0.563 for Elasticity/B-mode distance ratio (E/B ratio).

The radiologist acquired virtual touch strain images first. The longest lesion dimensions on both the elasticity image and the corresponding B mode image were measured to get a distance ratio (E/B ratio). Then virtual touch tissue imaging and quantification (VTIQ) SWE was performed. The image display setting used colors ranging from dark blue, representing the lowest stiffness, to red, representing the highest stiffness (0–125 kPa). The system calculated the median shear wave elasticity values of regions of interest (ROI) placed in the lesion in kPa (kPa_{median}) and the SWV_{median} values in meters per second (m/s).

Subsequently, all patients received ultrasound-guided core needle biopsies with a 14G Bard magnum needle using a co-axial technique. The elasticity values from the machine and the final pathological result by a pathologist were recorded for analysis.

R-software and MedCalc were used for the statistical analysis. Cohen's kappa (k) and McNemar test were used for estimating BI-RADS agreements and comparing the details of the BI-RADS classifications between the primary radiologist and the breast radiologist, with significance deemed at a p-value<0.050. Sensitivity, specificity, predictive values, likelihood ratios, and areas under the curve (AUC) were estimated for single type and combined elastography. The optimal cut-off values for SWV_{median} and kPa_{median} were calculated using the maximum Youden index. Malignancy was defined as an E/B ratio ≥1 for strained elastography and above the cut-off from the Youden index for SWE. The AUC values were calculated and compared by DeLong et al.'s theory.

Results

A total of 151 breast lesions composed of 119 BI-RADS 4A and 32 BI-RADS 4B lesions were included in the study. Three BI-RADS 4A lesions were excluded due to inadequate elastographic images, resulting in 148 lesions in 141 patients left for analysis. The histologic features are shown in Table 1. Patients with breast cancer or high-risk lesions were approximately ten years older than those with benign lesions (58.9±10.5 years vs 48±10.6 years of age) with statistical significance at p-value<0.001. The tumor sizes were similar between the benign and malignant lesions (mean±S.D., 1.2±0.5 cm).

The BI-RADS classification agreement using B-mode ultrasound between the general radiologist and the breast radiologist was moderately high (k=0.545, p-value ≤0.001). Only lesion shape, margin, and vascularity were statistically significantly different (Table 2). Two lesions originally classified by a general radiologist as BI-RADS 4C were re-classified by breast radiologist to be 4A and 4B and proved to be fibroadenoma and invasive ductal carcinoma after biopsy.

Table 1 Histologic features of breast tissue lesions in the study patients (N=148)

Histologic feature	No. of lesions (%)
Benign	
Fibroadenoma	74 (50.0)
Fibrocystic change	19 (12.8)
Intraductal papilloma	14 (9.5)
Stromal fibrosis	10 (6.8)
Sclerosing adenosis	6 (4.1)
Fat necrosis	2 (1.4)
Normal breast tissue	2 (1.4)
Chronic inflammation	1 (0.7)
Reactive lymph node	1 (0.7)
Total	**129 (87.2)**
High risk	
Lobular carcinoma in situ (LCIS)	2 (1.4)
Atypical ductal hyperplasia (ADH)	1 (0.7)
Total	**3 (2.0)**
Malignant	
Invasive ductal carcinoma	9 (6.1)
Ductal carcinoma in situ (DCIS)	4 (2.7)
Adenoid cystic carcinoma	1 (0.7)
Invasive solid papillary carcinoma	1 (0.7)
Mucinous carcinoma	1 (0.7)
Total	**16 (10.8)**

The elasticity values were significantly different between the benign and malignant groups. The median E/B ratio for benign (0.9) was statistically significantly lower than that for malignancy (1.2) at p-value<0.001. The SWE findings were consistent between the benign and malignancy groups, with medians of kPa_{median} (4.2 and 7.2) and SWV_{median} (1.2 m/s and 1.6 m/s), respectively, as shown in Figure 1.

Table 3 shows the cut-off values and diagnostic performance of the various elastography parameters for differentiating between benign and malignant breast lesions. Using the cut-off value of E/B ratio ≥1, the sensitivity of

63.0% and specificity of 78.0% were moderately high, while the negative predictive value (NPV) of 93.0% was very high. The cut-off values to provide high sensitivity and specificity for kPa_{median} and SWV_{median} were $kPa_{median} \geq 7$ and $SWV_{median} \geq 1.28$ m/s, respectively. When the positive E/B ratio and SWV_{median} were combined as a cut-off value, the specificity increased to 93.0% with a high NPV of 92.0% but lowered sensitivity of 47.0% for differentiating between benign and malignant breast lesions.

As shown in Table 4, using no elastography parameters as a reference in BI-RADS 4A, the diagnoses of benign breast lesions were minimally increased by 0.8%, 2.0%, and 2.5% for E/B ratio, kPa_{median}, and SWV_{median}, respectively. In contrast, the accuracy of identifying a malignancy was increased by approximately 10.0% for all adjunct elastography parameters for BI-RADS 4B lesions.

Table 2 Comparison of BI-RADS classifications based on B-mode ultrasound between the general radiologist and the breast radiologist

B-mode ultrasound	Primary BI-RADS by general radiologist	BI-RADS before biopsy by breast radiologist	p-value
Total	148	148	
Shape			0.006
Oval	110 (74.3)	88 (59.5)	
Round	1 (0.7)	0 (0.0)	
Irregular	37 (25.0)	60 (40.5)	
Margin			<0.001
Circumscribed	66 (44.6)	86 (58.1)	
Angular	10 (6.8)	2 (1.4)	
Microlobulated	31 (20.9)	40 (27.0)	
Indistinct	41 (27.7)	20 (13.5)	
Orientation			0.875
Parallel	123 (83.1)	125 (84.5)	
Not parallel	25 (16.9)	23 (15.5)	
Echo pattern			0.054
Anechoic	0 (0.0)	2 (1.4)	
Complex cystic and solid	10 (6.8)	14 (9.5)	
Hypoechoic	111 (75.0)	108 (73.0)	
Isoechoic	15 (10.1)	5 (3.4)	
Heterogeneous	12 (8.1)	19 (12.8)	
Posterior features			0.111
No posterior features	41 (27.7)	57 (38.5)	
Enhancement	66 (44.6)	65 (43.9)	
Shadowing	5 (3.4)	3 (2.0)	
Combined pattern	36 (24.3)	23 (15.5)	
Vascularity			<0.001
Absent	113 (76.4)	107 (72.3)	
Internal vascularity	9 (6.1)	6 (4.1)	
Vessels in rim	26 (17.6)	35 (23.6)	
BI-RADS			0.541
4A	116 (78.4)	116 (78.4)	
4B	30 (20.3)	32 (21.6)	
4C	2 (1.4)	0 (0.0)	

BI-RADS=breast imaging-reporting and data system

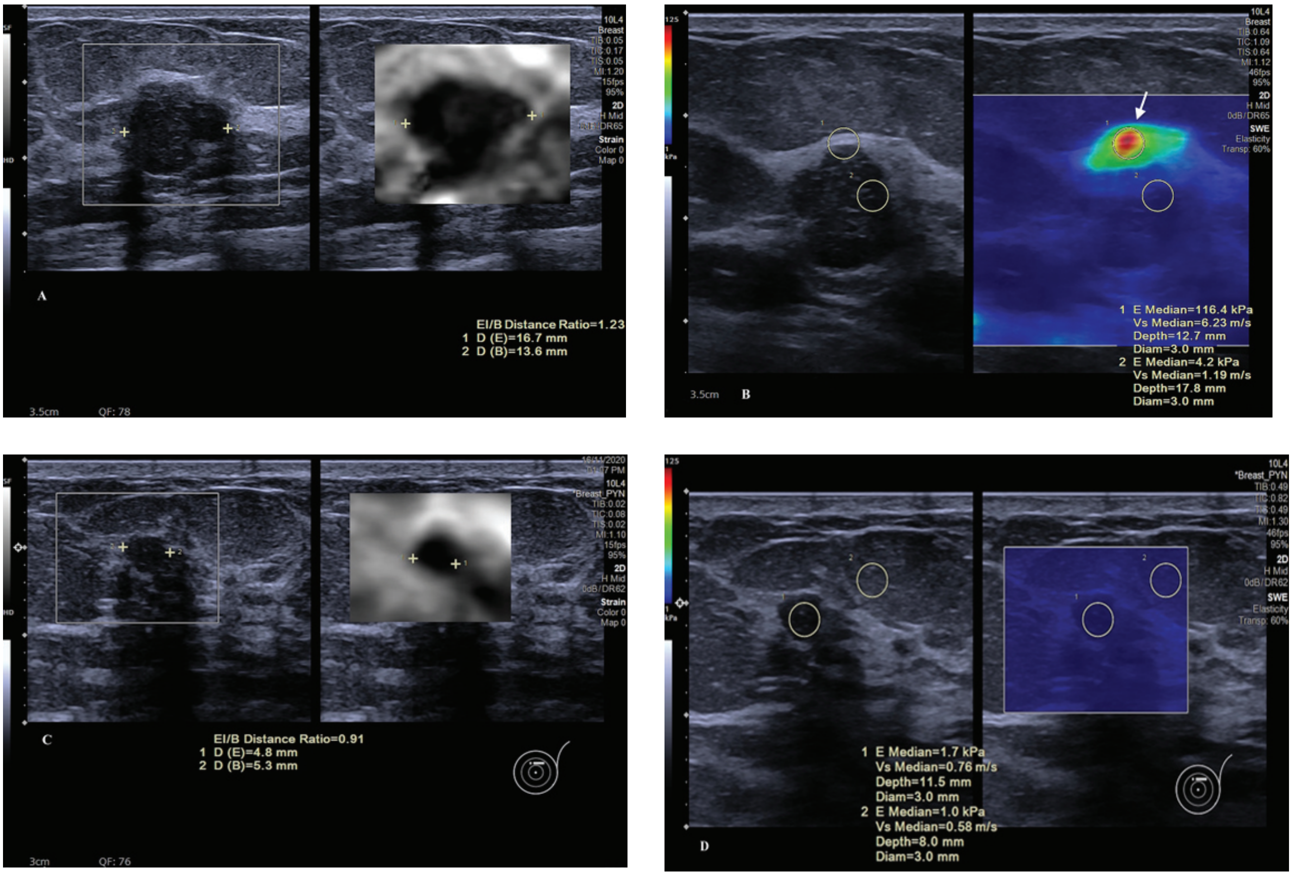

Figure 1 A screening mammogram of a 61-year-old woman showed increased size of an oval circumscribed mass at the lower inner quadrant of the left breast from a prior study (not shown). (A) The ultrasound shows an oval partially microlobulated margin hypoechoic mass at 8 o'clock, with an E/B ratio of 1.23. (B) The mass shows the most stiffness area at the anterior margin (arrow) with a kPa_{median} of 116.4 and SWV_{median} of 6.23 m/s. The histology reported an adenoid cystic carcinoma. (C-D) The other 51-year-old woman with a new small oval circumscribed isoechoic mass with an angular margin at the left 1 o'clock, with an E/B ratio of 0.91, and kPa_{median} and SWV_{median} of 1.7 and 0.76 m/s. Histology identified the mass as a fibroadenoma.

Table 3 Cut-off values and diagnostic performance of the various elastography methods for differentiating between benign and malignant breast lesions

Method	Cut-off value	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	AUC	PPV (%) (95% CI)	NPV (%) (95% CI)	LR^+ (95% CI)	LR^- (95% CI)
E/B ratio	≥1.0	63.0 (38-84)	78.0 (69-84)	0.703	29.0 (16-46)	93.0 (87-97)	2.81 (1.76-4.49)	0.48 (0.26-0.86)
kPa_{median}	≥7.0	47.0 (24-71)	82.0 (74-88)	0.748	28.0 (14-47)	91.0 (85-96)	2.66 (1.46-4.85)	0.64 (0.41-0.99)
SWV_{median} (m/s)	≥1.28	68.0 (43-87)	67.0 (58-75)	0.747	23.0 (13-36)	93.0 (86-98)	2.05 (1.39-3.03)	0.47 (0.24-0.93)
E/B ratio and SWV_{median}	≥1.0 and ≥1.28	47.0 (24-71)	93.0 (87-97)	0.702	50.0 (26-74)	92.0 (86-96)	6.79 (3.09-14.94)	0.57 (0.37-0.87)

CI=confidence interval, AUC=areas under the curve, PPV=positive predictive value, NPV=negative predictive value, LR=likelihood ratio, E/B=elasticity/B-mode distance ratio, kPa_{median}=median kilopascals, SWV_{median}=median shear wave velocity

Table 4 Using adjunct elastography parameters to downgrade BI-RADS 4A and increase the accuracy of BI-RADS 4B

BI-RADS	Elastography parameter	Benign Number (%)	Downgrade (%)
4A	None	110 (94.8)	Reference
	E/B ratio <1	86 (95.6)	0.8
	kPa_{median} <7	90 (96.8)	2.0
	SWV_{median} <1.28	72 (97.3)	2.5
BI-RADS	**Elastography parameter**	**Malignancy Number (%)**	**Increased accuracy (%)**
4B	None	13 (40.6)	Reference
	E/B ratio ≥1	10 (52.6)	12.0
	kPa_{median} ≥7	7 (50.0)	9.4
	SWV_{median} ≥1.28	10 (50.0)	9.4

BI-RADS=breast imaging-reporting and data system, E/B=elasticity/B-mode distance ratio, kPa_{median}=median kilopascals, SWV_{median}=median shear wave velocity

Discussion

In current radiological practice, the wide range of BI-RADS 4 lesions leads to a high biopsy rate with a high number of unnecessary biopsies due to the low positive predictive values. The BI-RADS classifications in our study were quite comparable to the standard ACR recommendations.

Tumor elasticity is an essential predictive factor for malignancies. Most benign lesions are soft, while malignant lesions are usually stiffer than the normal surrounding tissue. Our study found significantly different elasticities between benign and malignant lesions, with malignancies stiffer than benign tumors, corresponding to previous studies.[4,7] The diagnostic performance of ultrasound elastography is comparable between all sizes of cancers.[8] However, larger tumors may have higher values of elasticity than smaller tumors.

The mean SWVs for benign and malignant masses in a Tozaki et al. study were higher than our study, 2.68 m/s and 4.49 m/s (p-value<0.010), respectively.[9] Another study by Tang et al. using VTIQ also had similar results, with mean $SWV_{medians}$ of 3.09±1.04 m/s for benign and 5.89±1.92 m/s for malignant lesions (p-value<0.001).[10] Our lower median SWV_{median} values could be explained by noting that our study evaluated elasticity in only 4A and 4B BI-RADS 4 patients, with only 13.0% of malignancies and small tumor size. Those two studies included lesions with a higher percentage of malignancies ranging from 19.5-56.7%[9,10], while 83.0% of our benign lesions were fibroadenomas, fibrocystic changes, or intraductal papillomas, which can be softer than adenoses and fibroses, which were the primary benign lesions in the Zheng et al. study.[6]

Our cut-off values showed good specificity and NPV with low sensitivity, which helps in excluding benign from malignant lesions and thus results in lower biopsy rates. When combining the two elastography methods, the specificity improved with an insignificant change of the high NPV. Both strain and shear wave elastographies added value to BI-RADS; the diagnostic accuracy improved for differentiation between benignity and malignancy, corresponding with several previous studies using different elastography types.[11-15] Using our suggested parameters, a negative E/B ratio and $SWV_{median,}$ a specific subgroup of BI-RADS 4A lesions, those with an oval shape and circumscribed margin could be downgraded to BI-RADS 3 with a high NPV. However, with these conditions, false negatives are still possible, and a mammogram with clinical correlation and short interval follow-up are still crucial in this group.

Mucinous carcinoma is a type of cancer that can be soft and can present as new circumscribed masses in older women. In our study, the SWV_{median} for mucinous carcinoma was 1.01 m/s lower than the 2.44 m/s in the Tozaki et al. study.[9] This type of cancer can show a specific stiff rim pattern in color mapping and the ROI should be placed at the lesion's margin to correctly determine the mass's actual stiffness.[16]

The strengths of our study were that the BI-RADS classifications used the standard classification, and all lesions were biopsy proven. However, there were also some limitations. Our research was performed in a subpopulation of BI-RADS 4 patients with a low percentage of malignancies that may not represent the typical elastography spectrum. A larger population with a wider variety of BI-RADS lesions is suggested for future studies.

Conclusion

Elastography is not the sole imaging technique for providing a definite diagnosis in breast masses. Using the cut-off values of E/B ≥1 and SWV_{median} ≥1.28 combined with B mode ultrasound can help to increase diagnostic accuracy and to differentiate benign and malignant breast lesions, thus leading to avoiding unnecessary biopsies. Adequately trained and experienced radiologists or sonographers are essential to successfully implement ultrasound elastography in clinical practice.

Conflict of interest

There are no potential conflicts of interest to declare.

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