Original Article

Three-dimensional and Two-dimensional Shear Wave Elastography: Associations of Quantitative Elasticity Values with Prognostic Factors of Breast Cancer

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Abstract

Background: The aim of the study was to investigate the correlation of three-dimensional (3D) and two-dimensional (2D) quantitative shear-wave elastography (SWE) with prognostic factors in invasive breast cancer. **Methods:** Ninety-four female patients with 94 breast lesions were tested using B-mode ultrasound and SWE. 3D and 2D quantitative SWE characteristics, including elastic modulus standard deviation (E_{SD}) and maximum elasticity (E_{max}), were evaluated. The pathological prognostic indicators for breast cancer were assessed, encompassing factors such as tumor dimensions, histological grade, lymph node involvement, the status of histologic biomarkers, and the classification of tumor subtypes. Associations between 3D and 2D quantitative SWE values and prognostic factors of breast tumors were analyzed. **Results:** The quantitative parameters E_{max} and E_{SD} exhibited a notable correlation with tumor size subgroups (3D: $P = 0.002$ and $P = 0.024$; 2D: $P = 0.003$ and $P = 0.008$), and had a positive correlation with tumor size (3D: E_{max} $P = 0.379$, $P = 0.0002$, E_{SD} $P = 0.234$, $P = 0.023$; 2D: E_{max} $P = 0.398$, $P = 0.000$, E_{SD} $P = 0.361$, $P = 0.004$). The E_{max} and E_{SD} of breast cancer patients exhibiting lymph node metastasis were markedly elevated in comparison to those without lymph node metastasis (3D: $P = 0.024$ and $P = 0.036$; 2D: $P = 0.031$ and $P = 0.011$). E_{max} and E_{SD} except for E_{SD} in 3D SWE were markedly elevated in Ki-67-positive breast cancers than in negatively expressed breast cancers (3D: $P = 0.033$ and $P = 0.105$; 2D: $P = 0.044$ and $P = 0.029$). Combined BIRADS and 3D and 2D quantitative parameters demonstrated moderate diagnostic efficacy in predicting lymph node metastasis (area under the curve = 0.714). **Conclusion:** 3D and 2D quantitative parameters E_{max} and E_{SD} demonstrate significant associations with prognostic factors in invasive breast cancer, including tumor size, lymph node involvement, and Ki-67 expression.

Keywords: Breast, elastography, prognostic factors, three-dimensional, ultrasound

Introduction

According to the 2024 cancer statistics report, breast cancer is the most prevalent cancer globally among women,[1] characterized by its heterogeneity in clinical, histological, and molecular features that influence prognosis and treatment.[2] The primary prognostic factors for invasive breast tumors are tumor size, histological grade, and lymph node stage. Carcinomas larger than 20 mm, high nuclear grade, and positive lymph node status typically indicate aggressive biological behavior, characterized by high recurrence and low survival rates.[3,4] Biological markers such as estrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptor 2 (HER2) and Ki-67 index help anticipate treatment response and patient prognosis. In addition, classifying disease subtypes–luminal A, luminal B, HER2-enriched, and triple-negative breast cancer (TNBC)–is crucial. This classification is contingent on fluorescence *in situ* hybridization (FISH) or immunohistochemical results of ER, PR, HER2, and Ki-67 expression.[5]

Ultrasound elastography serves as an important diagnostic instrument for the evaluation of tissue rigidity. Current

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research indicates that strain elastography enhances US by effectively distinguishing benign from malignant breast lesions.[6] While, its accuracy is significantly influenced by the degree of tissue compression and compressibility, leading to considerable interobserver variability.[7] In comparison, shear-wave elastography (SWE) evaluates the rigidity of tissues quantitatively. Studies suggest that SWE offers high reproducibility, both inter- and intraobserver agreement, and can improve the specificity of breast cancer US examinations while maintaining sensitivity.[8]

Three-dimensional (3D) US provides a more precise evaluation of diseases, adjacent anatomical structures, and treatment responses.[9,10] Recent research demonstrated that 3D US characters, including the intratumoral vascularization index and the retraction pattern on the coronal plane, are valuable for anticipating breast cancer prognosis.[11] 3D SWE offers detailed elastographic data on masses, allowing for 3D visualization of mass heterogeneity and the stiffest regions. It demonstrates acceptable interobserver agreement and enhances diagnostic accuracy for breast conditions.[12] However, only mean elasticity values have been linked to breast cancer prognosis.[13] No research has examined the maximum elasticity (E_{max}) and standard deviation values obtained from 3D SWE in relation to histological prognostic indicators or breast cancer tumor subtypes.

This study aimed to investigate potential correlations between invasive breast cancer prognostic factors and elasticity characteristics (E_{max} and elastic modulus standard deviation [E_{SD}]) measured using two-dimensional (2D) and 3D SWE.

Materials and Methods

Patients

The retrospective study received approval from the institutional review board of our organization (approval number: KY2017-123), and written informed consent was obtained from all the participating women. The protocol followed the tenets of the Declaration of Helsinki.

Between December 2019 and September 2021, this study evaluated 432 patients at an academic institution in China, each with a single lesion, using B-mode US and 2D and 3D shear wave elastography (SWE) before undergoing US-guided core needle biopsy or surgical excision of breast masses. Exclusion criteria were established [Figure 1]. Exclusion criteria explanation: (1) Breast ductal carcinoma *in situ*: Ductal carcinoma *in situ* (DCIS) is a noninvasive breast cancer with different behavior and prognosis than invasive types. To maintain data consistency and relevance in studies on invasive breast cancer prognosis, DCIS cases should be excluded. (2) Patients with implants: Breast implants may compromise US image quality and interpretation, reducing diagnostic accuracy, so this group was excluded to maintain study consistency. (3) Women with substandard images: To maintain the diagnostic reliability of the study, patients with substandard images were excluded. (4) Underwent breast surgery and had a family history of breast cancer: These patients may present with more complex clinical and imaging scenarios. To reduce this complexity, they were excluded. (5) Pregnant or breastfeeding: Physiological changes may interfere with US parameter measurement. (6) Breast masses >3 cm: Lesions larger than

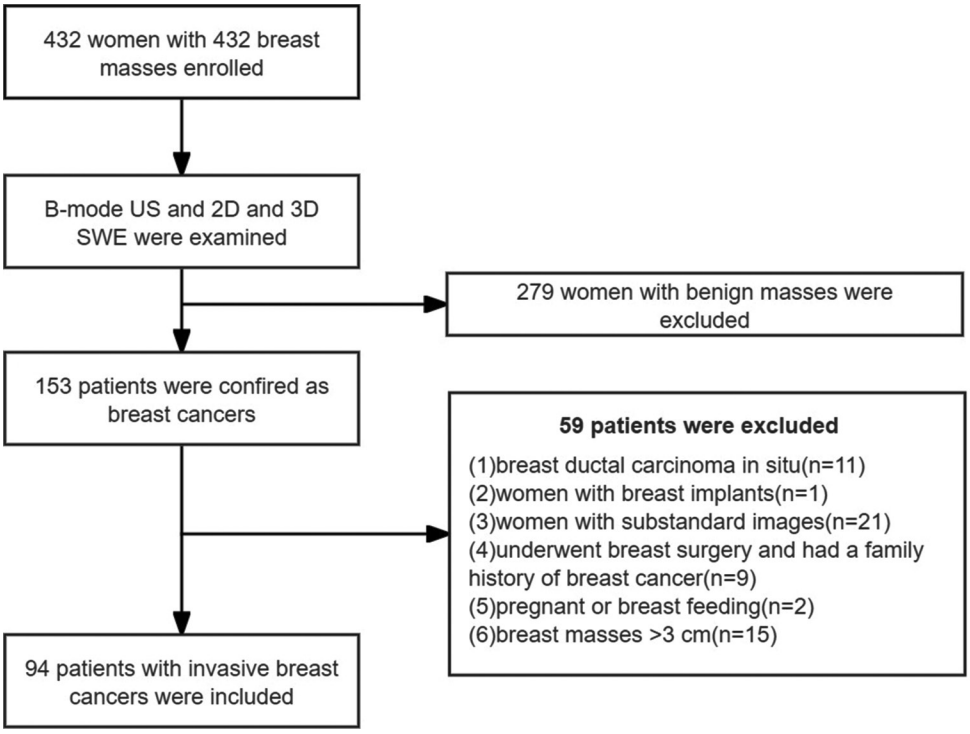

Figure 1: Flowchart of patients included. 2D: Two-dimensional, 3D: Three-dimensional

3 cm were removed as the maximum range of SWE could not fully encompass these larger lesions. Of all the patients, 66 (70%) were symptomatic, with 33 having palpable masses, 27 experiencing breast pain, and 6 presenting with nipple discharge. An experienced pathologist with two decades of expertise in breast pathology conducted the histopathological evaluation of breast nodules. An analysis of 94 patients with an average age of 47.5 years (range 33–80 years), with pathologically confirmed invasive carcinoma in 94 breast masses, was conducted.

Ultrasound examination

The US and 2D/3D SWE images were acquired utilizing an Aixplorer US system (SuperSonic Imagine, Aix-en-Provence, France) Two breast radiologists, each with 3–5 years of breast US and elastography expertise, conducted the imaging. Clinical history, mammography results, and histopathological data were unavailable during the US examination. A 4- to 15-MHz linear-array transducer was utilized for both 2D US and SWE imaging, while a 5- to 16-MHz mechanical volumetric transducer was employed for 3D SWE imaging.

The grayscale US characteristics of breast masses were evaluated on 2D images obtained from two orthogonal planes, following BI-RADS US guidelines. The largest dimension of the tumor was assessed using B-mode images, and breast nodules were classified into three size categories: 1–10 mm, 10–20 mm, and 20–30 mm. Subsequently, 2D SWE images were captured on identical imaging planes while maintaining the patient's position unchanged. The pressure applied was just enough to maintain skin contact over the lesion. On SWE, the square region of interest (ROI) was configured to encompass the tumor and adjacent normal tissue visible on B-mode. The US transducer was positioned over the mass for stabilization before capturing the SWE image for measurements.[14] Each pixel was color-coded, ranging from 0 kilopascals (kPa) (dark blue, representing softness) to 180 kPa (red, indicating hardness). Following 2D SWE acquisition, 3D volumetric SWE data were rebuilt and presented in both multi-slice and multi-planar formats. Volumetric imaging was automatically conducted using a sectorial mechanical transducer with a slow-tilt motion and a sweep angle of 10°–30°, and data were stored for subsequent analysis.

Image analysis

Two radiologists, who had 5–10 years of experience in both breast US and elastography, analyzed all images without access to clinical, mammographic, or pathological information independently. They were not involved in the acquisition of the US images.

Conflicts were settled through mutual agreement. For quantitative analysis, the E_{max} and E_{SD} on 2D and 3D SWE of all tumors were measured. Each mass underwent three distinct SWE acquisitions, and the average elasticity values were utilized for analysis. For 2D SWE, the built-in ROI (Q-Box TM) was configured to encompass both the mass and the adjacent rigid tissue or halo on SWE-mode images. The calculated standard deviation and E_{max} were recorded in kPa. For 3D SWE, quantitative variables were assessed across three orthogonal planes [Figure 2]. A 2-mm² Q-Box was used as a measurement ring to identify the most rigid area for E_{max}. Another Q-Box was set to include the entire lesion and the surrounding halo on the SWE image that contained the tumor's maximum equatorial plane and E_{SD} was measured.

Pathological analysis

Breast masses were surgically removed in the study group, with specimens processed per standard guidelines. Tumor sizes were recorded and categorized into three groups: 1–10 mm, 10–20 mm, and 20–30 mm. Cancers were histologically classified following the World Health Organization classification.

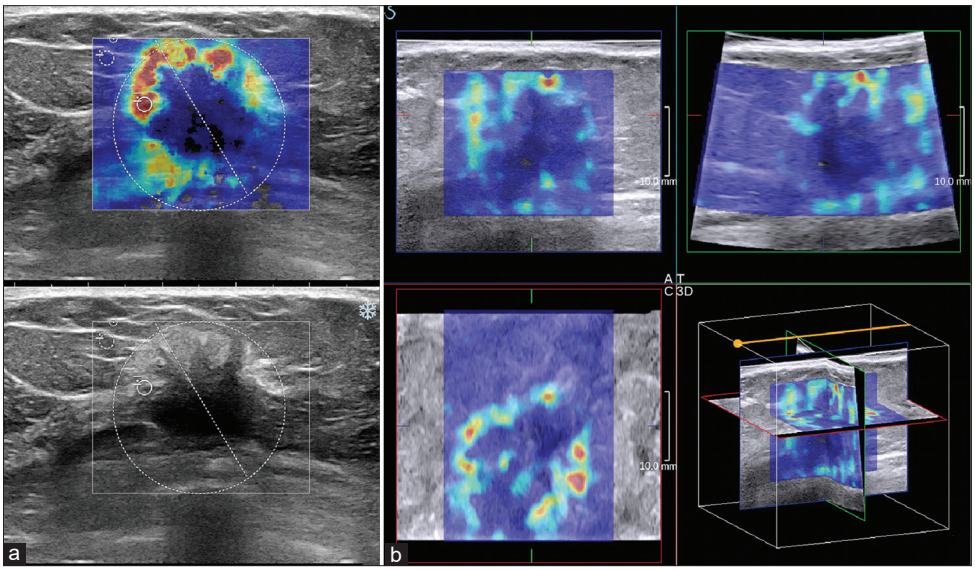

Figure 2: Invasive ductal carcinoma in a 56-year-old woman. Both 2D SWE (a) and 3D SWE (b) show an inhomogeneous hard mass and surrounding tissue. Elasticity features were assessed across three orthogonal planes. E_{max} and E_{SD} were measured

Invasive carcinoma histological grades were evaluated based on the Elston and Ellis system.[15] Lymph node status was deemed positive if histopathological analysis of the excised lymph node revealed any size of metastatic involvement.

The avidin-biotin complex immunohistochemistry method was employed to assess ER, PR, HER2, and Ki-67. ER and PR statuses were evaluated based on the Allred scoring system,[16] with expression levels below 10% deemed negative and 10% or higher considered positive. The Ki67 index was positive for expression levels of 20% or more and negative for levels below 20%. Immunohistochemistry was used to classify HER2. Tumors with scores of 0 or 1+ were classified as negative, while those with a score of 3+ were classified as positive. Tumors were classified as negative with scores of 0 or 1+ and as positive with a score of 3+. Tumors with a 2+ score underwent FISH analysis. An experienced pathologist with 15 years in breast, unaware of the clinicopathological features and outcomes of the patients, made the histologic diagnoses.

Tumors were categorized into four subtypes depending on IHC or FISH assessments of ER, PR, HER2, and Ki-67: (a) Luminal A: Characterized by ER-positive and/or PR-positive, HER2-negative, and Ki-67 <20%; (b) Luminal B: Defined as ER-positive and/or PR-positive, HER2-negative with Ki-67 ≥20%, or ER and/or PR-positive, HER2-positive regardless of Ki-67 levels;(c) HER2-enriched: Identified by ER-negative, PR-negative, and HER2-positive status; (d) TNBC: Defined as ER-negative, PR-negative, and HER2-negative status.[17]

Statistical analysis

Statistical methods utilized SAS software (version 9.1.3; SAS, Cary, NC, USA). Nonnormally distributed measures were reported as medians and quartiles, with group comparisons conducted via the rank sum test. The Mann–Whitney *U*-test was utilized to compare the two groups, while the Kruskal–Wallis test was employed to assess differences among three or more groups. The Chi-square test or Fisher's exact test was used to evaluate categorical variables. Frequencies and percentages were applied to express rank information. Spearman's rank correlation analysis was utilized to investigate the communication between variables. A multivariate logistic regression analysis was employed to fit the joint analysis model of multiple indicators. The receiver operating characteristic curve was devised, and the area under the curve (AUC) was measured. The specificity, sensitivity, positive predictive value, negative predictive value, and overall accuracy of each model were evaluated. AUC differences between diagnostic models were assessed employing the Delong test, with a statistical significance level of $P < 0.05$.

Results

Breast masses

The study included 94 female patients with invasive breast cancers, with a mean tumor size of 18.64 ± 6.45 mm (range, 7–30 cm). Among the 94 invasive breast cancer cases, histological types were distributed as follows: invasive ductal carcinoma (88 cases, 93.6%), mucinous carcinoma (three cases, 3.2%), invasive lobular tumor (two cases, 2.1%), and invasive papillary tumor (one case, 1.1%).

Quantitative SWE features

Using 3D SWE, the E_{max} was 172.40 ± 51.77 kPa (range: 41–263 kPa), significantly higher than the 2D SWE value of 141.86 ± 59.66 kPa (range: 36.3–300 kPa) ($P = 0.000$). The SD elasticity measured by 3D SWE was 21.84 ± 10.89 kPa (range: 5.9–60.4 kPa), showing no significant difference from the 22.15 ± 10.86 kPa (range: 5.6–62.4 kPa) measured by 2D SWE ($P > 0.05$).

Relationship between two-dimensional and three-dimensional SWE characteristics and tumor size

Significant differences in E_{max} values were detected across the three distinct size groups of breast cancer on 2D and 3D SWE (2D $P = 0.003$, 3D $P = 0.002$). The E_{max} values for the 20–30 mm group on 3D SWE demonstrated notable distinctions in comparison to the other groups (all $P < 0.05$). In addition, E_{SD} values on 2D and 3D SWE demonstrated notable distinctions among the three breast cancer size groups (2D $P = 0.008$; 3D $P = 0.024$, respectively). The E_{SD} values for the 20-30 mm group significantly differed from those of the 1 to 10 mm group on 2D and 3D SWE (all $P < 0.05$) [Table 1]. A mild correlation was observed between tumor size and 2D and 3D SWE parameters, indicating that the elasticity values of large tumors tend to be higher (all $P < 0.05$) [Figure 3].

Table 1: Comparison of elasticity values in kilopascals among tumor size groups on two-dimensional and three-dimensional shear wave elastography acquisitions

Tumor size group (mm)	*n*	2D E_{max}, medians (IQRs)	*P*	2D E_{SD}, medians (IQRs)	*P*	3D E_{max}, medians (IQRs)	*P*	3D E_{SD}, medians (IQRs)	*P*
1–10	5	86.9 (64.75)	0.003	14 (9.45)	0.008	108.1 (68.40)	0.002	11.8 (5.25)	0.024
10–20	53	128 (65.20)		18.5 (9)		166.7 (58.00)		18.9 (11.9)	
20–30	36	144.85 (116.32)		21.8 (17.5)		191.95 (74.90)		21 (14.08)	
Comparison		*P**		*P**		*P**		*P**	
1–10 versus 10–20		0.095		0.142		0.105		0.098	
10–20 versus 20–30		0.079		0.15		0.048		0.612	
1–10 versus 20–30		0.006		0.014		0.005		0.023	

*The *P* values have been adjusted for multiple comparisons using the Bonferroni correction method. 2D: Two-dimensional, 3D: Three-dimensional, IQR: Interquartile range, E_{SD}: Elastic modulus standard deviation, E_{max}: Maximum elasticity

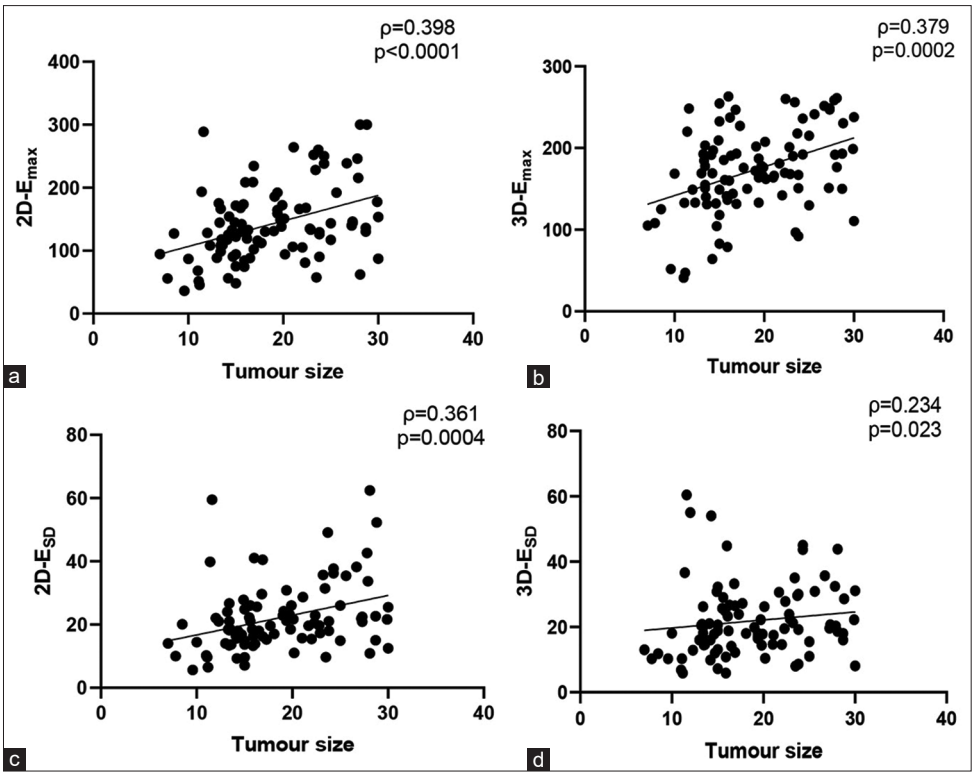

Figure 3: The relationship between tumor size and two-dimensional and three-dimensional SWE characteristics. The trend line indicates a positive correlation between tumor size and tissue elasticity, suggesting that larger tumor size is associated with increased elasticity value. (a) Correlation between 2D Emax and tumour size; (b) Correlation between 3D Emax and tumour size; (c) Correlation between 2D ESD and tumour size; (d) Correlation between 3D ESD and tumour size

Association between two-dimensional and three-dimensional SWE features and lymph node status

Significant differences in lymph node status were observed with both E_{max} and E_{SD} values on 2D and 3D SWE [Figure 4]. The elasticity value is higher in breast cancer with lymph node metastases. Table 2 displays the diagnostic efficacy of B-mode US and its combination with SWE features for predicting lymph node metastasis. The AUC for BI-RADS evaluation using only B-mode US was 0.657, with the optimal cutoff between categories 4b and 4c. The sensitivity and specificity were 74.4% (29/39) and 54.5% (30/55), respectively. Incorporating SWE parameters into B-mode US slightly enhanced the AUC, especially when combined with all 2D and 3D SWE features, while there were no notable distinctions (all $P > 0.05$). Adding 2D E_{max} to B-mode US showed a trend towards improved specificity, but there were no notable distinctions (60% vs. 54.5%, $P = 0.488$).

Association between two-dimensional and three-dimensional SWE features and additional prognostic factors

Table 3 shows the associations between histologic grades, molecular markers status, and tumor subtypes with 2D and 3D SWE features. E_{max} values on both 2D and 3D SWE were notably higher in Ki-67-positive tumors compared to Ki-67-negative ones (2D $P = 0.044$, 3D $P = 0.033$) [Figure 5]. E_{SD} on 2D SWE was notably elevated in Ki-67-positive masses versus Ki-67-negative masses ($P = 0.029$), whereas there were no notable distinctions on 3D SWE ($P = 0.105$). There was no significant correlation between SWE features and tumor subtypes ($P > 0.05$). There was no significant correlation between SWE features and histological grade ($P > 0.05$).

Discussion

This study utilized SWE quantitative features (E_{max} and E_{SD}) from both 3D and 2D SWE to evaluate their correlations with prognostic characters and tumor subtypes in invasive breast carcinoma. Our study identified that larger tumor size, positive lymph nodes, and Ki-67 positivity correlate with increased maximum and standard deviation on 3D and 2D SWE. In addition, the addition of SWE features to B-mode US, especially comprehensive 2D and 3D data, demonstrated good diagnostic efficacy in predicting lymph node metastasis.

3D and 2D SWE have demonstrated significant potential in distinguishing benign from malignant breast lesions and play a crucial role in minimizing false-positive biopsies and neoadjuvant chemotherapy treatments.[12,18,19] Cha *et al*.[20] demonstrated that in multivariate regression analysis, a higher elasticity value on 2D SWE correlated with Ki-67 positive, metastasis of axillary lymph node, and density of micro-lymphatics. According to Yoo *et al*.,[21] tumor stiffness estimated by SWE demonstrated a significant correlation with

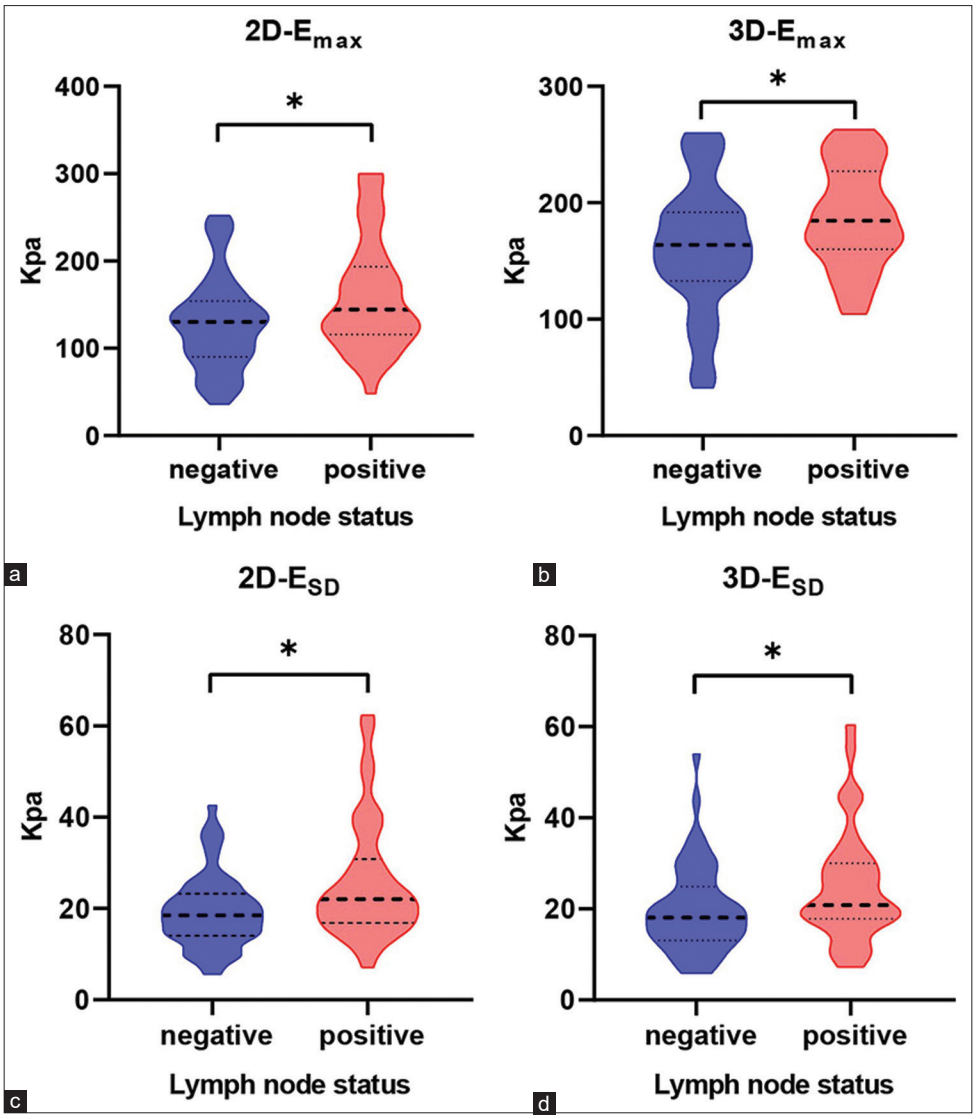

Figure 4: The distribution of the elasticity parameters (E_{max} and E_{SD}) were significantly different between the positive and negative lymph node status (two-dimensional: $P = 0.031$ and $P = 0.011$; three-dimensional: $P = 0.024$ and $P = 0.036$). *denotes statistical significance ($P < 0.05$)

both tumor hypoxia and histologic biomarkers. However, research on the effects of 3D SWE on breast tumor prognosis is still in its infancy. According to Kang *et al*.,[13] 3D and 2D SWE demonstrate that elevated Emean values correlate with adverse prognostic factors in invasive breast carcinoma. An *ex vivo* study demonstrated the potential of 3D multiparametric US to characterize the biopathology of breast cancer.[22] Our study similarly found a significant relationship between quantitative elasticity values and prognostic parameters of breast carcinoma. This study is the first to associate E_{max} and E_{SD} on 3D SWE of breast cancer with prognostic factors.

Previous research identified E_{max} as the most effective quantitative SWE feature for diagnosing breast cancer.[23] Our study found that E_{max} values on 3D SWE were considerably higher than those on 2D SWE for identical breast tumors, aligning with earlier studies.[24] The velocity of shear waves exhibits a strong sensitivity to external compressive forces.[24] A convex 3D probe, due to its greater weight, may exert more pressure compared to a 2D probe. Artefactual stiffness from external compression typically manifests near the skin surface in elastic imaging. Applying sufficient US gel to the 3D probe and gently positioning it on the skin surface can effectively minimize stress artifacts. E_{SD} can quantify lesion heterogeneity, a crucial factor in breast cancer prognosis and treatment response.[25] 3D SWE offers a complete tumor volume assessment, unlike the single-plane view on 2D SWE. Elastographic data from the 3D SWE volume, including the unique coronal plane, can be visualized and quantitatively evaluated, reducing the chance of missing tumor heterogeneity. 3D SWE-derived SD may more accurately represent the tumor mass's heterogeneity.

Our study identified significant variations in E_{max} and E_{SD} values across breast cancer groups of different sizes using both 2D and 3D SWE. In addition, a mild positive correlation was

Table 2: Diagnostic performances of B-mode ultrasound and B-mode ultrasound combined with shear wave elastography in predicting lymph node metastasis

Parameter	Threshold*	AUC	*P*	Sensitivity	Specificity	PPV	NPV	Accuracy
B-mode ultrasound category	>4B	0.657	NA	74.4 (29/39)	54.5 (30/55)	53.7 (29/54)	75.0 (30/40)	62.8
2D E_{SD}	≥21.4	0.654	0.966	56.4 (22/39)	69.1 (38/55)	56.4 (22/49)	69.1 (38/55)	63.8
2D E_{max}	≥169.6	0.631	0.669	38.5 (15/39)	83.6 (46/55)	62.5 (15/24)	65.7 (46/70)	64.9
3D E_{SD}	≥17.25	0.628	0.650	79.5 (31/39)	45.5 (25/55)	50.8 (31/61)	75.8 (25/33)	59.6
3D E_{max}	≥191.95	0.703	0.750	48.7 (19/39)	76.4 (42/55)	59.4 (29/32)	67.7 (42/62)	64.9
+2D SWE								
E_{SD}	≥0.449	0.703	0.168	61.54 (24/39)	72.73 (40/55)	61.54 (24/39)	72.73 (40/55)	68.1
E_{max}	≥0.401	0.684	0.354	74.4 (29/39)	60.0 (33/55)	56.9 (29/51)	76.7 (33/43)	66.0
E_{SD} + E_{max}	≥0.431	0.702	0.224	64.1 (25/39)	70.9 (39/55)	61.0 (25/41)	73.6 (39/53)	68.1
+3D SWE								
E_{SD}	≥0.289	0.689	0.215	89.7 (35/39)	40.0 (22/55)	51.5 (35/68)	84.6 (22/26)	60.6
E_{max}	≥0.318	0.675	0.523	87.2 (34/39)	47.3 (26/55)	54.0 (34/63)	83.9 (26/31)	63.8
E_{SD} + E_{max}	≥0.311	0.689	0.255	87.2 (34/39)	47.3 (26/55)	54.0 (34/63)	83.9 (26/31)	63.8
+2D and 3D SWE								
E_{SD} + E_{max}	≥0.478	0.714	0.132	56.4 (22/39)	83.6 (46/55)	71.0 (22/63)	73.0 (46/63)	72.3

*Threshold was the optimal cut-off, yielding maximal sum of sensitivity and specificity. The + before 2D SWE and 3D SWE indicates effect of adding that SW elastographic feature to the original BI-RADS category masses. *P* value was that to test the null hypothesis that there is no change in AUC with the addition of the SW elastographic feature (McNemar test). B-mode ultrasound category was defined according to the BI-RADS classification for ultrasound. 2D: Two-dimensional, 3D: Three-dimensional, SWE: Shear wave elastography, AUC: Area under the curve, NPV: Negative predictive value, PPV: Positive predictive value, NA: Not available, BI-RADS: Breast Imaging Reporting and Data System, SW: Shear wave, E_{SD}: Elastic modulus standard deviation, E_{max}: Maximum elasticity

Table 3: Relationships between shear wave elastography values and pathologic features of 94 invasive breast cancer

Characteristics	*n*	2D E_{max}, medians (IQRs)	*P*	2D E_{SD}, medians (IQRs)	*P*	3D E_{max}, medians (IQRs)	*P*	3D E_{SD}, medians (IQRs)	*P*
Histologic grade									
I	6	106.60 (87.85)	0.088	17.9 (6.17)	0.105	162.50 (111.98)	0.563	19.70 (13.27)	0.438
II	39	143.40 (69.70)		21.7 (12.2)		172.00 (56.90)		20.80 (12.90)	
III	39	132.80 (75.50)		20.5 (9.9)		175.90 (94.10)		19.50 (13.60)	
Molecular marker									
ER									
Negative	24	124.65 (77.43)	0.591	19.35 (8.27)	0.9	159.60 (86.13)	0.55	19.55 (19.85)	0.979
Positive	70	133.85 (70.47)		20.30 (11.70)		173.95 (55.68)		19.85 (11.55)	
PR									
Negative	20	116.80 (101.27)	0.449	18.10 (12.60)	0.605	157.45 (84.82)	0.449	18.50 (13.98)	0.446
Positive	74	133.95 (70.47)		20.95 (10.28)		173.95 (60.88)		20.10 (12.08)	
HER-2									
Negative	59	136.00 (68.40)	0.509	19.60 (11.10)	0.953	168.5 (67.7)	0.631	19.20 (14.00)	0.848
Positive	35	130.00 (73.30)		20.10 (8.00)		175.9 (52.8)		19.80 (13.70)	
Ki-67									
Negative	18	113.10 (63.25)	0.044	16.75 (8.18)	0.029	150.50 (83.13)	0.033	18.40 (8.75)	0.105
Positive	76	137.10 (65.65)		21.00 (10.18)		176.50 (64.72)		20.05 (14.38)	
Molecular subtype									
Luminal A	15	112 (40)	0.139	17.30 (6.40)	0.255	154.90 (43.40)	0.404	16.50 (10.60)	0.208
Luminal B (HER2+)	24	132.80 (60)		18.5 (7.5)		187.20 (91.50)		19.6 (8.4)	
Luminal B (HER2−)	40	144.45 (82.88)		22.70 (13.30)		181.40 (40.83)		20.25 (12.80)	
TN	5	126.00 (70.70)		21.00 (4.1)		167.00 (70.35)		30.00 (14.35)	
HER2	10	128.5 (87.07)		20.00 (13.58)		149.90 (112.75)		19.9 (21.38)	

2D: Two-dimensional, 3D: Three-dimensional, ER: Estrogen receptors, PR: Progesterone receptors, HER2: Human epidermal growth factor receptor 2, TN: Triple-negative, IQRs: Interquartile ranges, E_{SD}: Elastic modulus standard deviation, E_{max}: Maximum elasticity

found between tumor size and SWE parameters (E_{max} and E_{SD}) in both 2D and 3D SWE. Larger breast nodules corresponded to higher elasticity parameter values. Consistent with previous research, SWE stiffness was primarily influenced by tumor size.[13,26] Research on a human breast cancer model found that tumor rigidity, assessed via SWE, increased with tumor

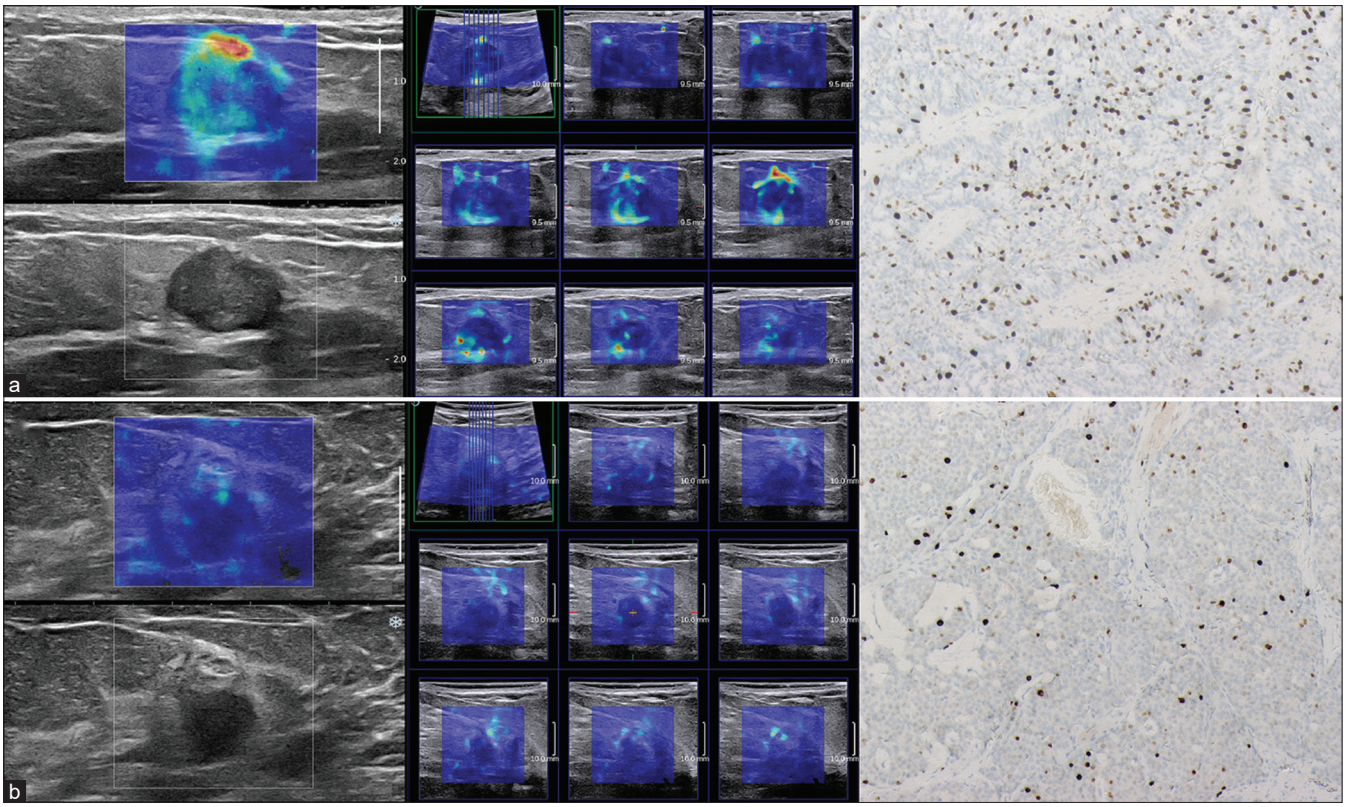

Figure 5: (a) Two-dimensional (2D) and three-dimensional (3D) SWE showed a heterogeneously stiff mass, and the Ki67 index was positive (IHC, ×100). (b) 2D and 3D SWE showed a softer mass, and the Ki67 index was negative (IHC, ×100)

growth and showed a strong correlation with pathological size, attributing the stiffness increase to fibrosis.[27] The size of the tumor serves as a crucial prognostic indicator in cases of invasive breast cancer, with larger tumors (>20 mm) linked to more aggressive phenotypes, higher recurrence, and lower survival rates.[3,4] Our study found that E_{max} values on 3D SWE for the 20–30 mm group significantly differed from other groups, while E_{SD} values only differed significantly from the 1 to 10 mm group. E_{max} on 3D SWE may more correctly indicate the biological phenotype of breast tumors.

The lymph node stage is broadly recognized as a crucial prognostic parameter of invasive breast tumors, with lymph node positivity often indicating a more aggressive biological phenotype.[3,4] A noteworthy relationship between lymph node status and E_{max} was reported.[28] Evans *et al*.[26] indicated a statistically significant positive relationship between lymph node involvement and elevated mean stiffness values. Previous research focused on 2D SWE, lacking studies on the correlation between E_{SD} and breast tumor prognostic parameters. Our studies indicate a significant positive association between lymph node positivity and elevated E_{max} and E_{SD} values on 2D and 3D SWE. In addition, the integration of B-mode US with SWE features offers diagnostic value in predicting lymph node metastasis. Although statistical differences were not observed, the combined approach shows a tendency for improved AUC compared to grayscale US alone. SWE enhances tumor heterogeneity visualization but may be limited by probe pressure, patient positioning, and lesion depth, potentially affecting elasticity measurement accuracy and diagnostic efficacy.[24,29,30] Furthermore, the small sample size may bias results, limiting generalizability. Larger, more diverse studies are needed for robust conclusions. In conclusion, E_{max} and E_{SD} on 2D and 3D SWE may serve as auxiliary indicators for predicting lymph node metastasis.

Our study found that E_{max} and E_{SD} values were notably elevated in Ki67-positive breast cancers in 2D and 3D SWE, aligning with previous research.[13,21] The Ki-67 index shows the proliferation rate of breast tumor cells. High Ki-67 expression signifies aggressive tumor growth, and increased metastatic potential, and is connected with higher recurrence risk and poorer prognosis of breast tumor patients.[31] Consequently, breast cancers with greater hardness and heterogeneity often show elevated tumor cells and worse outcomes. Our study found that breast tumors with ER-positive, PR-positive, and HER2-negative exhibit higher elasticity values, with Luminal B (HER2-) cancers being relatively stiffer, and HER2 breast cancers showing slightly lower E_{max} values. However, these differences were not statistically significant. Similarly, Ganau *et al.* did not indicate any correlation between immunohistochemical markers and elasticity parameters.[32] Chamming's *et al*. have displayed in a mouse model that the rigidity of the tumor positively correlates with fibrous degeneration and inversely with tumor necrosis.[27] HER2-type breast cancers usually contain more necrosis

and a lower degree of pro-connective tissue proliferative response.[9] This may explain the slightly lower E_{max} in HER2 breast cancers. Au *et al.* found a significant association between lymph node metastasis and E_{max}, but not between the histology grade and elasticity parameters,[28] which is similar to our findings. However, Youk *et al*. found that higher mean elasticity values were associated with higher histology grades,[33] which is inconsistent with our findings. Barr attributed the stiffness of breast cancer to a pro-connective tissue proliferative response, and histological grade I breast cancer is thought to have a more pronounced pro-connective tissue proliferative response than grade III breast cancer.[30] This is not consistent with the findings of Youk *et al*.[33] A larger sample size and further studies are needed.

The study had several limitations. Due to the retrospective design and small subject population, there may have been some selection bias in this study. Future study with a larger sample size and prospective analysis is required to validate our findings. In addition, this study did not evaluate inter- and intraobserver variability in elasticity measurements, as the images were evaluated in agreement by two radiologists. The interobserver agreement for interpreting 3D and 2D SWE features is reported to be significant, demonstrating strong reliability in quantitative elasticity measurements.[12] Moreover, lesions larger than 3 cm were removed from this study as the maximum range of SWE could not fully encompass these larger lesions. Finally, the study was conducted over a relatively short follow-up period, and long-term follow-up studies are needed to assess recurrence and survival rates for clearer prognostic insights.

Conclusion

Both 3D and 2D SWE indicate that higher max and SD elasticity values are associated with larger tumor size, lymph node-positive, and Ki-67-positive, with the exception of the relationship between E_{SD} on 3D SWE and Ki-67 expression. In addition, adding SWE features to B-mode US demonstrated good diagnostic efficacy in predicting lymph node metastasis. Both 3D and 2D quantitative parameters E_{max} and E_{SD} are associated with the prognostic factors of invasive breast cancer. Future studies with larger sample size are needed to confirm these findings.

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Conflicts of interest

There are no conflicts of interest.

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